

EFFECTS OF DEVELOPMENTS IN SYNTHETIC GENOMICS

HEARING BEFORE THE COMMITTEE ON ENERGY AND COMMERCE HOUSE OF REPRESENTATIVES ONE HUNDRED ELEVENTH CONGRESS SECOND SESSION

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EFFECTS OF DEVELOPMENTS IN SYNTHETIC GENOMICS

THURSDAY, MAY 27, 2010

HOUSE OF REPRESENTATIVES,
COMMITTEE ON ENERGY AND COMMERCE,
Washington, DC.

The Committee met, pursuant to call, at 9:08 a.m., in Room 2123 of the Rayburn House Office Building, Hon. Henry A. Waxman [Chairman of the Committee] presiding.

Members present: Representatives Waxman, Markey, Pallone, Gordon, Eshoo, Barrow, Castor, McNERNEY, Barton, Shimkus, Pitts, Bono Mack, Burgess, Gingrey, Scalise, Griffith, and Latta.

Staff present: Phil Barnett, Staff Director; Bruce Wolpe, Senior Advisor; Karen Nelson, Deputy Committee Staff Director for Health; Ruth Katz, Chief Public Health Counsel; Naomi Seiler, Counsel; Robert Clark, Policy Advisor; Stephen Cha, Professional Staff Member; Allison Corr, Special Assistant; Eric Flamm, FDA Detailee; Greg Dotson, Chief Counsel, Energy and Environment; Lorie Schmidt, Senior Counsel; Alex Barron, Professional Staff Member; Melissa Cheatham, Professional Staff Member; Karen Lightfoot, Communications Director, Senior Policy Advisor; Elizabeth Letter, Special Assistant; Lindsay Vidal, Special Assistant; Earley Green, Chief Clerk; Jen Berenholz, Deputy Clerk; Mitchell Smiley, Special Assistant; Clay Alspach, Counsel, Health; Ryan Long, Chief Counsel, Health; and Andrea Spring, Professional Staff Member, E&E.

Mr. WAXMAN. The meeting of the committee will please come to order. While we expect to call on our witnesses and have them give us their testimony at ten o'clock, I did want to have this hour available for members to be able to make opening statements. I will make my opening statement and Mr. Barton will make his opening statement just before we begin the testimony. But I want to call on members who wish to make opening statements and to recognize them at this time for that opportunity. So let me—Mr. Burgess?

Mr. BURGESS. Well, Mr. Chairman, actually I didn't realize this was the arrangement. I will waive an opening statement in deference time for questions because of the firepower we have on our panel this morning. So I will waive the opening statement.

Mr. WAXMAN. OK. Very good. We are not going to give you extra time. We will just have—those are the rules of subcommittee. Any other members seek recognition for an opening statement? Yes, Mr. Latta?

Mr. LATTA. Well, thanks, Mr. Chairman. If I may, I would like to waive opening statement, just submit my opening statement for the record please, my written statement.

[The prepared statement of Mr. Latta follows:]

Congressman Robert E. Latta
The Committee on Energy & Commerce
Subcommittee on Oversight and Investigations
Opening Statement – For the Record
May 27, 2010

MR. CHAIRMAN; RANKING MEMBER BARTON: Thank you for holding this hearing on synthetic genomics. It is my understanding that much progress has been made in the field and that there are potential positive implications in the fields of health and energy.

I am particularly interested in the possible application of synthetic biology in the energy field. My district in Northwest Ohio is home to world-class research in photovoltaic solar cells and the use of synthetic genomics in such research is progress towards diversifying our nation's energy supply.

While this technology could have a significant positive impact on biofuels, vaccines, pharmaceuticals, and clean water, I do have some ethical concerns. One researcher noted that “the most remarkable thing about our synthetic cells is that its genome was designed in the computer and *brought to life* through chemical synthesis, without using any pieces of natural DNA.” I believe that life is sacred and that scientific

advancements in synthetic biology must be mindful of this. I am pleased that stakeholders are continuing to examine these ethical and societal concerns.

Furthermore, I hope that as technology continues to develop in the field of synthetic genomics, safeguards will be put in place to prevent deliberate misuse in the form of bioterrorism. While biological pathogens have numerous legitimate applications in scientific research and therapeutics, the U.S. needs to prevent the re-creation of known pathogens such as Polio, the Ebola virus, and smallpox to protect us.

Mr. Chairman, thank you, and I look forward to hearing the testimony from the witnesses on the panel today. [Yield Back]

Mr. WAXMAN. Certainly. We—without objection, we are going to allow all members to submit written opening statements and this is an opportunity for those who want to give their opening statements at this—in an oral presentation at the committee meeting. Gentleman from Georgia, Mr. Gingrey.

OPENING STATEMENT OF HON. PHIL GINGREY, A REPRESENTATIVE IN CONGRESS FROM THE STATE OF GEORGIA

Mr. GINGREY. Mr. Chairman, thank you. Certainly, I look forward to hearing from these high powered witnesses as my colleague from Texas, my physician colleague just said, in exploring these issues further. However, it seems a bit ironic that we are holding a hearing on the future of medicine and synthetic biology when the future of our health system, I submit, indeed is in doubt.

A new study by Towers Watson found that one in six employers are likely to reduce employment and retirement plan contribution, such as 401(k)s, to pay for health reform. Forty-three percent of employers are likely to eliminate or reduce retiree medical programs because of this bill that we just passed. Ninety percent of employers believe healthcare reform will increase their organization's healthcare costs. Employers like AT&T are already filing billion dollar losses with the SEC.

Today, we should be meeting to explore why the Democrats health reform bill is hurting so many employers and subsequently, their employees. Such a hearing might also explore how spending trillions of dollars to turn our healthcare over to government bureaucrats may indeed very—may ruin the very market we need to produce groundbreaking new treatments like these witnesses are going to describe to us in this hearing today.

With that, Mr. Chairman, I will yield back my remaining time.

Mr. WAXMAN. Thank you. The gentleman yields back his time. Mr. Pitts.

OPENING STATEMENT OF HON. JOSEPH R. PITTS, A REPRESENTATIVE IN CONGRESS FROM THE COMMONWEALTH OF PENNSYLVANIA

Mr. PITTS. Thank you, Mr. Chairman and thank you for scheduling this hearing. Synthetic biology or synthetic genomics has been in the headlines recently with the news last week that Dr. Venter, who is testifying this morning, has developed the first self-replicating cell to be made from synthesized DNA. Advances in synthetic biology or synthetic genomics have potential applications across a wide variety of fields, healthcare and energy and the environment, to name a few, and synthetic genomics can already be used to produce medications and may possibly aid in tissue reconstruction.

In the future, these techniques could be used to create biofuels or lessen pollution and while these are exciting prospects, I think we all need to learn more about this science of synthetic biology and synthetic genomics. I also think we should carefully investigate the moral, the ethical issues, as well as public health and safety issues, that advances in the field are raising and I look forward to hearing from our distinguished witnesses, learning from them today. Thank you, Mr. Chairman and I yield back.

Mr. WAXMAN. Thank you very much, Mr. Pitts. Mr. McNerney, do you wish to make an opening statement?

Mr. MCNERNEY. Thank you, Mr. Chairman and I want to thank the panel for coming—what a distinguished list of speakers and they have made tremendous advances in the field and a lot more to come. Of course, there is always the risk that is associated with these sort of advances and we want to make sure that we are on good standing with those risks but the potential for good, in my opinion, outweighs the risk at this point, as long as we keep mindful of that, and I just want to say I am a little disappointed that our colleague from Georgia decided to make this into a political spectacle, but that is what happens in this committee.

But welcome aboard. I look forward to your testimony and thank you.

Mr. WAXMAN. Thank you, Mr. McNerney.

Any other member wish to be recognized for the purpose of giving an oral opening statement? We are going to recess until ten o'clock. We will then begin the hearing, with opening statements from the chairman and the ranking member, the chairman of the two subcommittees that have a specific interest in this, the energy and environment subcommittee and the health subcommittee and the chairman and the ranking members of those subcommittees as well and then we were going to call on this very distinguished panel.

So we are going to recess now and all other members will have an opportunity to put an opening statement, in writing, in the record. We are in recess until ten o'clock.

[Recess.]

OPENING STATEMENT OF HON. HENRY A. WAXMAN, A REPRESENTATIVE IN CONGRESS FROM THE STATE OF CALIFORNIA

Mr. WAXMAN. The meeting of the committee will come to order.

The scope and depth of scientific research in America is unrivaled. As a result, we and others around the world live healthier lives and enjoy of the many advantages of modern technology. As policymakers, we want to foster promising discoveries, while ensuring that research is conducted and applied responsibly. To this end, it is our job to understand what the science does and does not entail. We need to separate splashy headlines and science fiction scenarios from the reality of what scientists are doing and where their research might lead.

Last Thursday, we learned that researchers had taken a major step forward by synthesizing the entire set of genetic instructions for a bacteria and using it to reprogram another bacterial cell. Observers as diverse as the American Society for Microbiology and a Vatican City newspaper have noted the potential benefits of this research. Today, we will learn more about this and other advances in synthetic biology, the science of constructing or adapting DNA cells and tissues. We will explore potential applications to improve health, protect the environment, and meet our energy needs.

We have also discussed the ethical implications and the need to responsibly manage risks. Of course, this field did not just spring up. Scientists have been harnessing the power of DNA for decades.

While most research involves one celled organisms, like bacteria or yeast, the results are far reaching. For example, in 1982, the FDA approved human insulin from a gene inserted into yeast cells. Genetic engineering has been used to make human growth hormone, hepatitis vaccine, and other products and as we will hear, newer methods are already leading to important medical applications. Synthetic biology also has a potential to reduce our dependence on oil and to address climate change. Research is underway to develop microbes that would produce oil, giving us a renewable fuel that could be used interchangeably with gasoline, without creating more global warming pollution. Research can also lead to oil eating microbes, an application that, as the Gulf spill unfortunately demonstrates, would be extremely useful. The promise of synthetic biology does not diminish the importance of it being conducted and applied responsibly, as is true whenever science advances.

We must weigh and manage the safety, health, and environmental risks posed by this evolving science. Fortunately, this assessment can build on existing regulatory frameworks and I am pleased to see that President Obama has just asked his bioethics commission to conduct a thorough analysis of these issues. I look forward to hearing more today from three leaders in the field of synthetic biology, Dr. Craig Venter, Dr. Jay Keasling, and Dr. Drew Endy. They will explain their work and its current and potential applications.

Dr. Kaebnick of The Hastings Center will offer a framework for discussing the ethical questions related to synthetic biology, questions about risk, and also about fundamental beliefs about life and we also look forward, as always, to learning from Dr. Fauci on NIH's role in synthetic biology and how the agency's current approach can adapt to advances in the science. Before we call on our witnesses, I want to recognize the ranking member of the committee, Mr. Barton, for opening statement.

[The prepared statement of Mr. Waxman follows:]

**Statement of Chairman Henry A. Waxman
Committee on Energy and Commerce Hearing
“Effects of Developments in Synthetic Genomics”
May 27, 2010**

The scope and depth of scientific research in America is unrivalled. As a result, we, and others around the world, live healthier lives and enjoy the many advantages of modern technology.

As policymakers, we want to foster promising discoveries, while ensuring that research is conducted and applied responsibly. To this end, it is our job to understand what the science does and does not entail. We need to separate splashy headlines and science-fiction scenarios from the reality of what scientists are doing and where their research might lead.

Last Thursday, we learned that researchers had taken a major step forward by synthesizing the entire set of genetic instructions for a bacteria and using it to “reprogram” another bacterial cell. Observers as diverse as the American Society for Microbiology and a Vatican City newspaper have noted the potential benefits of this research.

Today, we will learn more about this and other advances in synthetic biology – the science of constructing or adapting DNA, cells, and tissues. We will explore potential applications to improve health, protect the environment, and meet energy needs. We will also discuss the ethical implications and the need to responsibly manage risks.

Of course, this field didn't just spring up - scientists have been harnessing the power of DNA for decades. While most research involves one-celled organisms like bacteria or yeast, the results are far-reaching. For example, in 1982, the FDA approved human insulin from a gene inserted into yeast cells. Genetic engineering has been used to make human growth hormone, hepatitis vaccine, and other products. And as we'll hear, newer methods are already leading to important medical applications.

Synthetic biology also has the potential to reduce our dependence on oil and to address climate change. Research is underway to develop microbes that would produce oil, giving us a renewable fuel that could be used interchangeably with gasoline without creating more global warming pollution. Research could also lead to oil-eating microbes, an application that, as the Gulf spill unfortunately demonstrates, would be extremely useful.

The promise of synthetic biology does not diminish the importance of its being conducted and applied responsibly. As is true whenever science advances, we must weigh and manage the safety, health, and environmental risks posed by this evolving science. Fortunately, this assessment can build on existing regulatory frameworks. I'm pleased to see that President Obama has just asked his Bioethics Commission to conduct a thorough analysis of these issues.

I look forward to hearing more today from three leaders in the field of synthetic biology. Dr. Craig Venter, Dr. Jay Keasling and Dr. Drew Endy will explain their work and its current, and potential, applications. Dr. Kaebnick of the Hastings Center will offer a framework for discussing the ethical questions related to synthetic biology – questions about risk, and also about fundamental beliefs about life. And I look forward, as always, to hearing from Dr. Fauci on NIH's role in synthetic biology and how the agency's current approach can adapt to advances in the science.

**OPENING STATEMENT OF HON. JOE BARTON, A
REPRESENTATIVE IN CONGRESS FROM THE STATE OF TEXAS**

Mr. BARTON. Good. Thank you, Chairman Waxman. I sincerely do appreciate you scheduling this hearing today. It is good to have a hearing about positive—at least what I consider to be potentially very positive developments in the field of bioresearch. We are going to hear today from scientists at the Craig Venter Institute and others. They announced, not too long ago, that they had created the first living organism with a completely synthetic genome. Just amazing. They have used more than 1,000 sections of preassembled units of DNA to create an altered version of a bacteria that causes arthritis in goats. It is an odd thing to recreate, but they have done it. Their version is a little jazzier than the original, apparently. It is blue and includes the scientists' names in code. I want the next one to be red. OK? You have done one for the blue side, now do one for the red side.

I hear that there are many potential applications of this new technology for both energy and health innovations. In fact, the first biotech patent is for a microorganism that could clean up oil spills and that is really good news. Companies are also looking into enhancing algae to make it a better producer of ethanol or perhaps even to produce oil. One of our witnesses today has reengineered a yeast to help produce an antimalarial drug. I am also told that this technology could be especially valuable in producing vaccines for fast mutating viruses, such as influenza.

We must not only review the potential benefits of this new technology though, Mr. Chairman. We must also look at the possible ethical and safety implications. It is very important that safeguards prevent new viruses from being created and accidentally, or maybe even intentionally, released to infect humans or animals. It also creates additional bioterrorism risk if terrorists erode nations, using the technology for bad purposes. Although we are a long way from using synthetic genomes to create large life forms, this is also a long-term concern.

I hope to hear from the witnesses what sort of voluntary and mandatory safeguards and procedures should be put into place to ensure that we see only the benefits from these exciting new developments. Mr. Chairman, the rest of my statement, which is three pages, is about the healthcare bill. I am not going to spoil this hearing by reading all that because this is an important hearing and I wanted to be positive and focus on the positive implications. I do hope though in the near future though, Mr. Chairman, that we could be in to schedule some hearings about the implications of the new healthcare law. We are having a Republican meeting this afternoon, briefing at one o'clock in the Visitor's Center. So I am not going to put that into the record. I will simply say that hopefully in the future, we can hold some hearings on that new bill, new law.

But for this hearing today, I am sincerely appreciative of our witnesses. I think this is a good thing for the committee to be doing and look forward to positive interaction in the question and answer period.

Mr. WAXMAN. Thank you very much, Mr. Barton. I want to recognize the chairman of our health subcommittee, Mr. Pallone, for an opening statement.

OPENING STATEMENT OF HON. FRANK PALLONE, JR., A REPRESENTATIVE IN CONGRESS FROM THE STATE OF NEW JERSEY

Mr. PALLONE. Thank you, Mr. Chairman and thank you for calling what I consider a very important hearing. It is certainly going to be beneficial to hear directly from our witnesses on the effects of the developments in synthetic genomics. Advancements in science over the past several decades have led to exciting developments in medical treatments and today, we will learn about the current state of research to effectively synthesize or modify DNA, explore the applications of this research related to health and energy and discuss the frameworks for ensuring compliance with ethical and regulatory guidelines.

Research in the '70s and '80s related to recombinant DNA technology led to one of the most notable early successes for advances in drug development. In 1982, human insulin became the first of many FDA approved medicines which utilizes technology and later, the first recombinant vaccine was produced for the hepatitis B virus. New strategies related to combining engineering and biological techniques have strengthened advancements and science related to genetic cellular and tissue level biology and one of our witnesses today, Dr. Jay Keasling—hope I am pronouncing it properly—will testify about the innovative work he has done related to production of the anti-malarial drug, artemisinin. The disease malaria kills over a million people each year and it second only to tuberculosis in its impact on world health. This disease spread by mosquitoes is endemic in 90 countries and infects one in ten of the world's population and malaria is a major cause of death globally and a significant threat to the health of children. The drug Artemisinin is currently far too expensive for the people in developing countries who need it the most and advances in drug production has the potential to dramatically lower the price of this treatment, which will be notable advance for global health.

Our good friend and frequent witness from the NIH, Dr. Fauci—I hope I am pronouncing it—is also here with us today. Dr. Fauci, the director of the National Institute of Allergy and Infectious Diseases, will discuss the role of the NIH and research using recombinant DNA and synthetic biology. NIAID supported research have sequenced the complete genomes of hundreds of disease-causing organisms, such as malaria, tuberculosis, and seasonal and pandemic influenza. NIAID has been a leader in providing support to research applying recombinant DNA technologies, genomics, and other related disciplines to the study of these infectious diseases and we will also hear from Dr. J. Craig Venter of the J. Craig Venter Institute about the exciting work he and his colleagues have recently published this week and how this team believes their work will lead to greater application in vaccine and energy production.

Advancements in science must always be balanced by strict and appropriate ethical guidelines. Clearly, there are many who remain concerned that someone with nefarious intentions could take ad-

vantage of new technologies and create a biological weapon and we are fortunate to have with us today Gregory Kaebnick, a research scholar at The Hastings Center. The Center is an independent, nonpartisan, nonprofit research institute that has been studying ethical issues in medicine, health policy, medical research, and biotechnology since 1969. Mr. Kaebnick will address concerns related to biosafety, deliberate misuse and governance of bioethical issues, including the role of NIH recombinant DNA advisory committee and the institutional biosafety committees at research universities that receive federal funding.

These boards, along with President Obama's presidential commission for the study of bioethical issues, provide important oversight and safety measures that accompany our advancements in scientific discovery.

Again, thank you, Mr. Chairman. I know that this is, frankly, I think, very interesting material but not easily understood and I know that, you know, we need to do more hearings like this and of course, it is—since it goes beyond health into energy and other issues, it is important that we have it at the full committee level. So thank you, Mr. Chairman.

Mr. WAXMAN. Thank you very much. Now I would like to recognize the ranking member of the subcommittee, the gentleman from Illinois.

OPENING STATEMENT OF HON. JOHN SHIMKUS, A REPRESENTATIVE IN CONGRESS FROM THE STATE OF ILLINOIS

Mr. SHIMKUS. Thank you, Mr. Chairman, and welcome to the panel. Synthetic genomes have a great potential to make advancements in health in humans, as well as reducing Americans dependent upon foreign energy and so I welcome you all here to help educate us. From perfecting drugs, detecting and preventing infections, strengthening human tissue and developing enzymes that break down plant waste and convert into biofuels, synthetic genomes hold a great potential in the health area.

There are some ethical and safety concerns we must remain mindful of as this technology advances but the opportunity for growth is certainly encouraging.

Having said that, I wish I was as magnanimous as my ranking member, but I have asked this question for about four weeks straight now for hearings on a healthcare law and I will use my time to address some concerns in that vein. You know, another week and another opportunity lost to address issues that are pressing in this healthcare law. The committee has seemingly dropped everything for this hearing, including cancelling a previously scheduled hearing, yet there has never, ever been a hearing on the actual health reform law that we passed.

Every day we are hearing from constituents with questions and concerns on how the new law will affect them and businesses, small and large, are trying to understand how they can keep their doors open and provide insurance to their employees. The state of Virginia recently estimated the impact of the unfunded mandate on states will be 40 percent more than their initial estimate. Will all states have similar unsustainable increases? The Medicare flier sent this week by the administrator highlights improvements of

Medicare Advantage. But the CMS actuary report says 50 percent of seniors will lose their Medicare Advantage plans and for the other 50 percent, CBO said their benefits will be gutted an average of \$816 per senior. How can we look at these seniors and tell them these are improvements? Last week, the administration taunted the tax incentives for small businesses and how it would provide relief to small firms. CBO says only 12 percent of businesses would see any relief at all, even with fewer eligible for the small tax credit and to get that full tax credit, you have 10 or less employees making an average of \$25,000 or less. This leaves 88 percent of the entire small business workforce employed at a small firm that won't get any tax credit at all.

I sent a letter to Chairman Pallone last week requesting a hearing on the impact on small business. We look forward to a response on that request in the near future. There was recently also a letter from Republicans on the committee, requesting a hearing with the CMS Actuary on the report. To my knowledge, we have not had a response. Could that have been on the schedule today? Can we, as members of this committee, honestly say these concerns in the public do not rise to the level of greater immediate importance? I am hopeful the committee will hold formal hearings. But we have asked on several occasions and our requests have been ignored.

Starting this afternoon at 1 p.m. in the Capitol Visitor's Center, the Republican Healthcare Solution Group will hold its first of a series of forums on the new health reform law. Today, we will have expert witnesses testifying on the true cost of the health reform law, as cost estimates continue to rise for families, businesses, and taxpayers as a whole. Press has been invited. We will be webcasting and Tweeting live, as well as posting the video on the hearing online. I would encourage anyone interested in the impact of this government takeover of healthcare to contact any office on the Republican side for more details. With that, Mr. Chairman, thank you and I yield back my time.

Mr. WAXMAN. Thank you very much, Mr. Shimkus. I would like to talk about the necessary war in Iraq, the deficits that we are experienced because of unpaid for tax credits for the upper income, and other very bad decisions made by the Republican administration, but that is not what this is all about. We have another hearing scheduled. This is May, 2010. We are a number of months off from an election. Had this been made 2009, you might have heard the same story. Seems like campaigns go on forever—

Mr. SHIMKUS. Would the chairman yield for one second?

Mr. WAXMAN. Sure.

Mr. SHIMKUS. Yes, I remember in the Medicare debate, when you continued to push for the Actuary to have a hearing here, after the fact. We are just asking—I am just doing the same thing that you did when you were in the minority and I think that when the CMS Actuary has an opportunity to give us the real numbers and we have asked numerous times that, you know, we—and there is issues out there that we could fix. We should do that.

Mr. WAXMAN. The gentleman and I—I would be pleased to discuss it with you further but I want to proceed with this—

Mr. SHIMKUS. Thank you, Mr. Chairman.

Mr. WAXMAN [continuing]. Hearing. Thank you for the points. Our witnesses today, Dr. J. Craig Venter is the president and founder of the J. Craig Venter Institute, the not-for-profit genomics research institute. He is also the founder and chief executive officer of Synthetic Genomics Incorporated.

Dr. Jay Keasling is a professor in the Department of Chemical Engineering and Bioengineering at the University of California Berkley. He is also acting deputy director of the Lawrence Berkley National Lab and chief executive officer of the DOE funded Joint BioEnergy Institute.

Dr. Drew Endy is an assistant professor in the Department of Bioengineering at Stanford University, president of the BioBricks Foundation and director of BioFab, the international open facility advancing biotechnology.

Dr. Gregory Kaebnick is a research scholar at The Hastings Center, a nonpartisan bioethics research institution. He is also editor of the Bioethics Journal, The Hastings Center report and Dr. Anthony Fauci is the director of the National Institute of Allergy and Infectious Diseases and the National Institutes of Health.

We are pleased to welcome all of you today at our hearing. It is the custom of all oversight hearings to ask that the witnesses testify under oath so I would like to ask if you would please rise and hold up your right hand.

[Witnesses sworn.]

Mr. WAXMAN. The record will indicate each of the witnesses answered in the affirmative. We are anxious to hear what you have to say. If you do want to comment on the health insurance plan adopted by the Congress, save that for another hearing. But we have got a lot of information that we want to learn about from you. Dr. Venter, why don't we start with you?

TESTIMONY OF J. CRAIG VENTER, PH.D., FOUNDER, CHAIRMAN AND PRESIDENT, J. CRAIG VENTER INSTITUTE; JAY D. KEASLING, PH.D., ACTING DEPUTY DIRECTOR, LAWRENCE BERKLEY NATIONAL LABORATORY; DREW ENDY, PH.D., ASSISTANT PROFESSOR, STANFORD UNIVERSITY, PRESIDENT, BIOBRICKS FOUNDATION; GREGORY E. KAEBNICK, PH.D., EDITOR, HASTINGS CENTER REPORT, ASSOCIATE FOR PHILOSOPHICAL STUDIES, THE HASTINGS CENTER; AND ANTHONY S. FAUCI, M.D., NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES, NATIONAL INSTITUTES OF HEALTH

TESTIMONY OF J. CRAIG VENTER

Mr. VENTER. Chairman Waxman, Mr. Barton, committee members, thank you for the opportunity to be here today. I will just make a few introductory comments to explain what it is we announced last week with our publication in science. We announced the first synthetic species. Its genome was read, encoded in the computer, as we have been doing since 1995. Now we have been able to reverse that process. We have been able to start with a digital code in the computer, four bottles of chemicals, and write the over one million letters of genetic code for this small microbe. We then were able to transplant that into a recipient cell. The syn-

thetic genome took over that cell and converted that cell into a new species. The only genome in that species is the synthetic genome. All the proteins there are made from that synthetic code and that is why we call it a synthetic cell. What it is not, it is not life from scratch. We used a living cell and converted it into a new cell, based on this synthetic genome. But it is the first cell to have its parent being a computer and this is the first, even though there has been a long trend, a real merging of the digital world and the biological world, we can now start in the digital computer and go out and write new software of life, the software's DNA.

This is a baby step, in our view. This is a proof of concept. This organism was not made for any other purpose, other than for the proof of concept. We have been working on this for 15 years, since we sequenced the first two genomes in history in 1995, trying to have the tools to understand a minimal cellular life. But over the course of that time, we have clearly become aware of other possibilities and uses for this powerful technology and we have been exploring that. I started, along with Hamilton Smith and two others, a new biotech company a few years back called Synthetic Genomics in La Jolla, California, aimed to build on these new tools, these new technologies. One of our partners is Exxon Mobil. We are trying to look at algae to make new sources of hydrocarbons that can go into the refineries, starting with carbon dioxide. We have seen, for this last month, a very visible reminder about oil coming out of the ground. We don't see CO₂ in the atmosphere but we can certainly see the oil on the water and the beaches in the Gulf.

I feel very strongly we need to wean ourselves off of oil. If we can start with carbon dioxide as the feed stock, it could be a tremendous advance. Looking at tens of thousands of species of algae, there is nothing out there that we found yet that has the power to get up to the billions of gallons of fuel that are needed. So the tools of molecular biology, the modern tools, including the ones we have just developed are going to be key to that success. We also see potentially next year's flu vaccine could come from these tools that we developed, not from the synthetic cell but the ability to write the genetic code and we have funding from NIH, actually from Dr. Fauci's institute, to start building the segments of all the flu viruses that we have been sequencing with funding from the NIH, we will have these on the shelf and we could very rapidly, we think in less than one day, build new vaccine candidates in contrast to the months that it currently takes. These could feed in. One of our partners is Novartis. They are building an NVCK cell facility that these new candidates could go into rapidly producing vaccines. These are powerful tools that give us a new way to look at the world.

The last thing I will mention is we, I think almost unprecedented in science, asked for ethical review of this research before we did the first experiments. This was back in 1997. This was done at the University of Pennsylvania. They published our results in *Science* in 1999. We have had ongoing discussion, trying to drive the discussion. We have had funding from the Sloan Foundation, along with MIT. The reports have been published looking at the security. In fact, many of my colleagues here have been looking at these issues and driving them. So the scientists, I think, not only are

being responsible, we are asking the questions before anybody else has.

We have worked with different administrations. In 2003, our early work was funded by the Department of Energy. The Secretary of Energy held a press conference with our announcement then of a synthetic virus. This work has been vetted in the past administration through the White House and came down on a side of open scientific publication, which I think is a real victory for science.

I have briefed the Administration and many members of Congress before our announcement. We think this is an important initial step in science, gives us some tools to go a long way. So Mr. Chairman, Mr. Barton, committee members, if you will incorporate—I ask my statement get incorporated into the record and thank you for the opportunity.

[The prepared statement of Mr. Venter follows:]

PREPARED STATEMENT OF
J. CRAIG VENTER, PH.D.
PRESIDENT, J. CRAIG VENTER INSTITUTE
BEFORE THE
U.S. HOUSE OF REPRESENTATIVES
COMMITTEE ON ENERGY AND COMMERCE
May 27, 2010

Mr. Chairman and Committee members, I welcome the opportunity to testify before you today. I am J. Craig Venter, Ph.D, President and Founder of the J. Craig Venter Institute (JCVI). The JCVI is a not-for-profit research institute in Rockville, MD and La Jolla, CA dedicated to the advancement of the science of genomics; the understanding of its implications for society; and communication of those results to the scientific community, the public, and policymakers. The JCVI is home to approximately 400 scientists and staff with expertise in human and evolutionary biology, genetics, bioinformatics/informatics, information technology, high-throughput DNA sequencing, genomic and environmental policy research, and public education in science and science policy. The JCVI is a 501 (c) (3) organization.

I am also the Founder and Chief Executive Officer of Synthetic Genomics Incorporated (SGI) a privately held company launched in 2005 to speed the commercialization of synthetic genomics technologies for a wide variety of applications including energy, the environment, and medicine.

In my testimony today I will first provide a brief overview of synthetic genomics, including answers to some key questions that I am often asked about this new technology. I will then briefly describe our recent accomplishment, and the 15 years of research that preceded it. Finally, I will discuss work to date on the ethical and societal implications of synthetic biology and review the ongoing policy discussions within the Federal Government.

OVERVIEW

Genomic science has greatly enhanced our understanding of the biological world. It is enabling researchers to "read" the genetic code of organisms from all branches of life by determining the sequence of the four letters that make up DNA. Sequencing genomes has now become routine, giving rise to thousands of genomes in the public databases. In essence, scientists are digitizing biology by converting the A, C, T, and G's of the chemical makeup of DNA into 1's and 0's in a computer. But can one reverse the process and start with 1's and 0's in a computer to define the characteristics of a living cell? We set out to answer this question.

In the field of chemistry, once the structure of a new chemical compound is determined by chemists, the next critical step is to attempt to synthesize the chemical. This would prove that the synthetic structure had the same function of the starting material. Until now, this has not been possible in the field of genomics. Structures have been determined by reading the genetic code, but they have never been verified by independent synthesis.

In 2003, JCVI successfully synthesized a small virus, approximately six thousand base pairs long, that infects bacteria. And by 2008, the JCVI team was able to synthesize a small bacterial genome, 580,000 base pairs long.

My team and I have now achieved the final step in our quest to construct the first synthetic bacterial cell. In a publication in *Science* magazine, Daniel Gibson, Ph.D. and a team of 23 additional researchers outline the steps to synthesize a 1.08 million base pair *Mycoplasma mycoides* genome, constructed from four bottles of chemicals that make up DNA. This synthetic genome has been "booted up" in a cell to create the first cell controlled completely by a synthetic genome.

The work to create the first synthetic bacterial cell was not easy, and took this team approximately 15 years to complete. Along the way we had to develop new tools and techniques to construct large segments of genetic code, and learn how to transplant genomes to convert one species to another. The 1.08 million base pair synthetic *M. mycoides* genome is the largest chemically defined structure ever synthesized in the laboratory.

While this first construct—dubbed *M. mycoides* JCVI-syn1.0—is a proof of concept, the tools and technologies developed to create this cell hold great promise for application in many critical areas. Throughout the course of this work, the team also contemplated, discussed, and engaged in outside review of the ethical and societal implications of their work.

The ability to routinely write the “software of life” will usher in a new era in science, and with it, new products and applications such as advanced biofuels, clean water technology, food products, and new vaccines and medicines. The field is already having an impact in some of these areas and will continue to do so as long as this powerful new area of science is used wisely. Continued and intensive review and dialogue with all areas of society, from Congress to bioethicists to laypeople, is necessary for this field to prosper.

ANSWERS TO SOME KEY QUESTIONS

I would like to give you an overview of the potential for the new field of synthetic genomics and the implications of our work to construct a synthetic cell by providing brief answers to a series of key questions.

How is synthetic genomics different than standard molecular biology/genetic engineering, etc?

Scientists have long been able to change and/or modify single genes or small sets of genes. Most genetic alterations that people know about today are through engineering of crops, which involves adding or altering less than 10 genes out of the tens of thousands that are contained in most organisms or plants. Synthetic genomics is different in that scientists start with digital information in the computer, which allows for the design of entire synthetic chromosomes to replace existing chromosomes in cells. The first self-replicating synthetic bacterial cell constructed by scientists at the JCVI has more than 1 million base pairs of DNA, almost 1,000 genes, and involved the complete replacement of genetic material in the cell. More detail about the construction of this cell may be found below in the section “Creation of a Synthetic Bacteria Cell,” and in the attachment *Gibson et al. 2010*.

Why construct a synthetic cell?

We believe that the ability to “write the genetic code”, as we describe synthetic genomics, will enable a better understanding of the fundamentals of living cells. It will also enable us to direct cells and organisms to perform jobs, such as producing clean water or new biofuels that natural species cannot currently do to the needed scale and efficiencies.

Is this research creating a synthetic bacterial cell “creating life from scratch”?

No. We do not consider this to be “creating life from scratch”; rather, we are creating new life out of already existing life using synthetic DNA to reprogram the cells to form new cells with functions that are specified by the synthetic DNA.

What are the potential applications of a synthetic cell? What is the impact of this area of science and the resulting technologies?

The work to create a synthetic cell will have a profound and positive impact on society in that it will enable a better understanding of the fundamentals of biology and of how life works. It will lead to new techniques and tools for advanced vaccine and pharmaceutical development, and will continue to enable the development of new biofuels and biochemicals. As well, these technologies could be used to produce clean water, new sources of food, textiles, human and veterinary drugs, bioremediation techniques, etc. More details on specific applications may be found below in the section “Beneficial Applications of Synthetic Genomics.”

I believe, along with my teams at JCVI and the company Synthetic Genomics Inc (SGI), that this science has the potential to be a major wealth driver for societies. A recent report, “Synthetic Biology: Scope, Applications and Implications,” from the Royal Academy of Engineering in the United Kingdom, states, “Synthetic biology has the potential to create another raft of major new industries, the development of which is likely to have profound implications for the future of the

UK, European and world economies.”

http://www.raeng.org.uk/news/publications/list/reports/Synthetic_biology.pdf

What are the risks associated with synthetic organisms? Do the risks of these technologies overshadow the potential benefits?

As with any new area of science, medicine or technology, synthetic genomics has the potential to be used for great societal benefit (biofuels, vaccines and pharmaceuticals, clean water, bioremediation, etc), but it could also be used for negative purposes. So called dual use technologies need to be carefully discussed and reviewed both at the government level (Federal, state and local) both in the US and globally, as well as in accessible forums for bioethicists, educators, students, media and the public to learn about the science and understand these risks and benefits.

My teams at both the JCVI and at SGI have, as the leaders of this field, been driving these ethical and societal implications since the beginning of the research (for nearly 15 years). The policy team at JCVI has completed study on options for governance of this field and is currently engaged in a study of the societal issues this work raises. Many other countries are reviewing and discussing this area of science and as such numerous reports and reviews have also been conducted. More detail may be found in the section below, “Ethical and Societal Implications/Policy Discussions about Synthetic Biology”.

Does this work have anything to do with humans/human research?

No. All synthetic genomics work to date, both at the JCVI and elsewhere, has focused on microorganisms. It is anticipated that given how little is known about human biology that no applications of this work will or should be attempted in humans. The way that this research will impact human lives is through the numerous applications such as new vaccines, pharmaceuticals, biofuels, etc.

What safeguards/controls are in place to protect against accidental environmental release?

This is an extremely important question for this research and as such has been a major focus for the researchers at JCVI and SGI. Building on the longstanding and successful history in molecular biology of millions of experiments engineering and using organisms such as *E. coli* to conduct research, JCVI and SGI researchers will be able to engineer synthetic bacterial cells so they cannot live outside of the lab or other production environments. This is done by, for example, ensuring that these organisms have built in dependencies for certain nutrients without which they cannot survive. They can also be engineered with so called “suicide genes” that kick in to prevent the organism from living outside of the lab or environment in which they were grown.

Has there been any review of this work by the US government, or by any other organizations?

The synthetic genomics research at JCVI has undergone review at the highest levels of the US government. Beginning in 2003 with the publication of the research at JCVI in constructing the synthetic virus phiX174 (“Generating a synthetic genome by whole genome assembly: phiX174 bacteriophage from synthetic oligonucleotides.” Smith et al, PNAS 2003 Dec 23;100(26):15440-5. Epub 2003 Dec 2.), and including the most recent research and publication on creating the first self-replicating synthetic bacterial cell, the work has been reviewed by White House offices including the Office of Homeland Security and Office of Science and Technology Policy, the National Science Advisory Board for Biosecurity (NSABB), the Department of Energy, the National Institutes of Health, and others. As well, the work has been reviewed by independent bioethics groups since 1997. Senior US government officials including those at the NIH were briefed and allowed to review our study prior to publication.

What, if any, types of legislation or regulation should be applied to this area of research?

We think that it is prudent, as is being proposed by the Department of Health and Human Services (HHS), to require DNA synthesis companies to screen synthesis requests against data on harmful agents. In 2004, JCVI’s Policy team, along with the Center for Strategic & International Studies (CSIS) and the Massachusetts Institute of Technology (MIT) were funded by the Alfred P. Sloan Foundation to conduct a series of workshops and public sessions over a 20-month period to discuss the biosecurity and biosafety implications of synthetic genomics. Over the course of the study, the group explored the risks and benefits of the emerging technology, as well as possible safeguards to prevent abuse, such as bioterrorism. In October of 2007 the group published their findings in a report, outlining options for the field and its researchers moving forward.

More recently, in December of 2008, JCVI received funding, again from the Alfred P. Sloan Foundation, to examine ethical and societal concerns that are associated with the developing science of synthetic genomics. The ongoing research is intended to inform the scientific community as well as educate our policymakers and journalists so that they may engage in informed discussions on the topic.

What are the next steps for this research at JCVI?

The work to create the first self-replicating, synthetic bacterial cell was an important proof of concept. The team at JCVI has learned much from the nearly 15 years it has taken to get to this successful stage. From this proof of concept experiment the team is now ready to build more complex organisms with useful properties. For example, many researchers, including scientists at SGI, are already using available sequencing information to engineer cells that can produce energy, pharmaceuticals, and industrial compounds, and sequester carbon dioxide. The team at JCVI is already working on its ultimate objective, which has been to synthesize a minimal cell that has only the machinery necessary for independent life. Now that a cell can be synthesized

from a synthetic genome, it now becomes possible for the team to test for the functionality of every essential gene in the genome. We can delete non-essential DNA regions from the synthetic genome and repeat transplantation experiments until no more genes can be disrupted and the genome is as small as possible. This minimal bacterial cell will enable a greater understanding of the function of every gene in a cell and a new vision of cells as understandable machines comprised of biological parts of known function.

Is this research patented?

Over the course of the 15 years it has taken to construct the first self-replicating synthetic bacterial cell, the team at JCVI has had to develop new tools and technologies to enable this research. SGI has funded the work at JCVI in exchange for exclusive intellectual property rights. SGI has filed 13 patent family applications on the unique inventions of the JCVI team. SGI believes that intellectual property is important for this kind of research and application development, as it is one of the best means to ensure that this important area of basic science research will be translated into key commercial products and services for the benefit of society. SGI intends to provide licenses to its synthetic genomics patents.

CREATION OF A SYNTHETIC BACTERIAL CELL

The ability to sequence or “read” an organism’s entire genome—the full repertoire of genes in that organism—has been possible for several decades and is now quite routine. Much can be learned about an organism by sequencing its genome. However, learning to write genetic code is crucial to truly understanding some of the most fundamental aspects of life. If scientists can write genetic code then it becomes possible to optimize certain functions in organisms that would be beneficial for society. With these ideas in mind, we set out to create a synthetic bacterial cell. The work has its roots in 1995 and 1999 publications on *Mycoplasma genitalium*, but the quest to develop the first synthetic bacterial cell began in earnest in 2003.

May 21, 2010 Science Publication

On May 21, 2010, the JCVI synthetic genomics team of nearly 25 researchers, led by me, Hamilton Smith, Clyde Hutchison, John Glass, and Dan Gibson, published results detailing the first cell constructed in the lab using only synthetic DNA. The work was published online in the journal *Science* and details the work to chemically synthesize the 1.08 million base pair genome of the bacterium *Mycoplasma mycoides*.

This and previous breakthrough work by JCVI researchers was funded by Synthetic Genomics Inc. The US Department of Energy also funded early work in this area, particularly the work to construct the synthetic phiX174 published in 2003.

Using previously published techniques and breakthroughs with the genetic system of yeast and of genome transplantation, the team put chemically synthesized pieces of the *M. mycoides* DNA into yeast which assembled the bacteria's genome. Then, the *M. mycoides* genome was transplanted into *Mycoplasma capricolum* and "booted up" to create a new synthetic version of *M. mycoides*.

Steps involved in building the synthetic *M. mycoides* are as follows:

1. First, the JCVI team designed 1,078 specific cassettes of DNA that were 1,080 base pairs long, with overlaps of 80 base pairs (bp) at their ends to aid in building the longer stretches of DNA. These were made according to JCVI's specifications by the DNA synthesis company, Blue Heron Biotechnology.
2. Then the team employed a three stage process using yeast to build the genome from these 1,078 cassettes. The first stage involves taking 10 cassettes of DNA at a time to build 10,000 bp long segments. In the second stage, these 10,000 bp segments are taken 10 at a time to produce eleven 100,000 bp long segments. Finally, all 11 segments are assembled into a complete synthetic genome as an extra chromosome in a yeast cell, by using yeast genetic systems.
3. The complete synthetic *M. mycoides* genome is then released from the yeast cell and transplanted into *M. capricolum* recipient cells that have had the gene for a restriction enzyme removed. Following incubation, viable *M. mycoides* cells are produced in which the only DNA present is the synthetic genome. These cells are controlled only by that synthetic genome.

Scientific Milestones on the Quest to Create the First Synthetic Bacterial Cell

1995: After sequencing the *M. genitalium* genome (published in 1995), my colleagues and I began work on the minimal genome project. This area of research, trying to understand the minimal genetic components necessary to sustain life, started with *M. genitalium* because it is the bacterium with the smallest genome known that can be grown in pure culture. This work was published in the journal *Science* in 1999.

2003: Drs. Venter, Smith, and Hutchison (along with JCVI's Cynthia Andrews-Pfannkoch) made the first significant strides in the development of a synthetic genome by assembling the 5,386 base pair genome of bacteriophage phiX 174. They did so using short, single strands of synthetically produced, commercially available DNA (known as oligonucleotides) and using an adaptation of polymerase chain reaction (PCR), known as polymerase cycle assembly (PCA), to build the phiX genome. The team developed methods that allowed the synthetic phiX to be produced in just 14 days. This work was published in the Proceedings of the National Academy of Sciences (PNAS).

2007: JCVI researchers led by Carole Lartigue, Ph.D., announced the results of work published in the journal *Science*, which outlined the methods and techniques used to change one bacterial species, *M. capricolum*, into another, *M. mycoides*, by replacing one organism's genome with the other's genome. Genome transplantation was the first essential enabling step in the field of synthetic genomics as it is a key mechanism by which chemically synthesized chromosomes can be activated into viable living cells.

January 2008: The second successful step in the JCVI team's effort to create a cell controlled by synthetic DNA was completed when Gibson et al. published in the journal *Science*, the synthetic *M. genitalium* genome.

December 2008: Gibson et al. published a paper in *Proceedings of the National Academy of Sciences (PNAS)* describing a significant advance in genome assembly in which the team was able to assemble in yeast the whole bacterial genome, *M. genitalium*, in one step from 25 fragments of DNA. The work was funded by the company Synthetic Genomics Inc. (SGI). At this point the team is still working to boot up the *M. genitalium* synthetic cell using all the knowledge gleaned from their previous work.

2009: JCVI researchers published results describing new methods in which the entire bacterial genome from *M. mycoides* was cloned in a yeast cell by adding yeast centromeric plasmid sequence to the bacterial chromosome and altered in yeast using yeast genetic systems. This altered bacterial chromosome was then isolated from yeast and transplanted into a related species of bacteria, *M. capricolum*, to create a new type of *M. mycoides* cell. This was the first time that genomes were transferred between branches of life—from a prokaryote to eukaryote and back to a prokaryote. The research was published by Lartigue et al. in *Science*.

SYNTHETIC GENOMICS AND SYNTHETIC BIOLOGY DEFINED

Synthetic genomics is a new capability that engages in the design and assembly of genes, chromosomes, and potentially entire multi-chromosome genomes. The basic units of construction are chemically synthesized oligonucleotides (called oligos). Oligos are short strings of DNA formed from the four nucleotide bases (i.e., A, C, G, and T).

Although the terms are sometimes used interchangeably, synthetic genomics differs from the more widely known synthetic biology in the scale of changes that can be made and in the kinds of experiments that it enables. Synthetic biology, by its community's view, is derived from engineering principles and is focused on the design and construction of biological parts (genes, pathways), devices (multiple parts), and systems (multiple devices). The chief aim of synthetic biology is to provide standardized sets of 'parts' that can be joined together in new ways in a living organism. Synthetic genomics technologies, on the other hand, provide the capability to build whole genomes and can examine how best to organize them.

While methods and tools for conducting synthetic biology have been available for many years, synthetic genomics is a completely new capability developed at JCVI. Our program in synthetic genomics has developed a set of techniques that are fundamental to engineering an organism in its entirety. Two key features of our synthetic genomics capabilities are: 1) rapid assembly of DNA molecules up to millions of base pairs in size (a million base pairs can code for ~1000 genes) and 2) “combinatorial” reconstruction of genomes, that is, novel genetic arrangements can be produced and assayed quickly. The application of rational engineering principles to the construction of combinatorial libraries (collections of pieces of DNA put together in different arrangements)—followed by high-throughput screens to select for optimal arrangements—ensures hundreds-to hundreds of thousands of competing designs can be examined in parallel.

One of the major advantages of synthetic genomics over classical biotechnology techniques—such as recombinant DNA—is that there is no need to have access to a physical supply of a particular DNA sequence. Sequence fragments are simply created *de novo* by chemical synthesis and assembled into entire chromosomes and organisms. This ability to synthesize (write) DNA and use it in the construction of new cells can catalyze a major change in what organisms can be engineered to do. Importantly, it will also increase our understanding of microbial life processes. Not only can new cells types be created but existing natural systems can be exhaustively probed to reveal the inner workings and properties displayed by living organisms.

BENEFICIAL APPLICATIONS OF SYNTHETIC GENOMICS

Synthetic genomics will make a unique or significant contribution as an enabling technology that is changing the nature of basic biological research; and as a powerful tool of applied biotechnology with the potential for developing new or improved applications for human health (including new pharmaceuticals and faster development of vaccines), biological sources of liquid transportation fuels, the manufacturing of other bio-based products, and environmental surveillance.

Synthetic genomics is today changing the nature of *basic molecular biological research*. As an enabling technology, DNA synthesis has already proved to be a significant time saver by shortening the time needed for experiments compared to time-consuming recombinant DNA techniques. As DNA synthesis becomes ever less expensive, researchers will be able to use synthetic genomics to rapidly change the DNA sequence of various genes or whole genomes, allowing them to understand basic cellular functions in a rigorous way. For example, various laboratories are beginning to use synthetic genomics (specifically, the combinatorial reconstruction of genomes) to understand the mechanisms of evolution at the molecular level, to define regulators of specific genes or gene pathways and to establish, at the molecular level, the minimal requirements for life. Without synthetic genomics, investigators can only manipulate one or at most a few genes in any given experiment, resulting in a relatively slow discovery

process.

These laboratory techniques can also be applied to beneficial products. Drugs, vaccines, and modified microbes for use in humans are all important targets of applied research using synthetic genomics. The capability to make subtle changes at the DNA sequence level may lead to more efficient research and production of *vaccines for human and animal health* and related *diagnostics*. Currently, scientists are working on ways to use synthetic genomics technologies for the mitigation of influenza epidemics with the eventual ability to generate vaccines more rapidly than they are currently being generated. These technologies could be applied to several steps in the vaccine development process, resulting in moderate to significant time savings compared to current methodologies. Additionally, the ability to assemble and mutate sequences rapidly could allow for the development of broadly protective vaccines against viruses that themselves are diverse and variable, such as the viral causative agents of severe acute respiratory syndrome (SARS) and hepatitis C.

The JCVI has recently been funded by the NIH to use our new synthetic DNA tools to build synthetic segments of every known flu virus so that we can rapidly build new vaccine candidates in less than 24 hours. We are also being funded to see if we can take sets of genes out of bacteria to design new antibiotic synthetic pathways to make chemical compounds that are currently too complex for chemists to make. With the extensive research already underway in this new field of synthetic biology, there will be thousands of new developments that we cannot imagine today.

DNA synthesis techniques have already been applied in research on new or improved drugs. For example, the antimalarial drug artemisinin is naturally produced in the plant *Artemisia annua* through a complex metabolic pathway that cannot feasibly be reconstructed in yeast using conventional biotechnological methods. Scientists have been able to synthesize an artemisinin precursor (which is then subject to chemical modification to make the final product) and are in the process of learning how to scale up this production to make the drug widely and relatively inexpensively available. This type of modification is likely to be applicable to a wide variety of drugs.

Synthetic genomics could also contribute to the search for *carbon-neutral energy sources*. A major application of synthetic genomics could be in overcoming biological barriers to cost-effective production of biofuels. There are several major initiatives in alternative or substitute fuel production research. One promising approach now is to engineer photosynthetic algae (either microalgae or blue-green algae) that are already relatively efficient at converting carbon dioxide into oils so that they carry out this process at a scale that is commercially viable.

While biofuels from algae may be the best current target for alternative fuels, *consolidated bioprocessing* (CBP) of cellulosic biomass to ethanol is a possible route as well, and may be preferable in some settings. Scientists are trying to engineer a single organism to include all the multiple steps needed to produce ethanol from cellulose. While the use of synthetic genomics to

produce all of the enzymes needed for CBP is not the only technique available, it is among the most promising. If successful, CBP might be able to produce ethanol at a cost competitive with gasoline.

Sometimes called “white biotechnology,” *biobased manufacturing* is becoming a reality. Plants and microbes are being engineered to produce raw materials that can be used to manufacture products that today are typically petroleum based. The expectation is that biologically based manufacturing will lead to more environmentally friendly products and methods of production. For example, the environmental impacts of plastic manufacturing might be lessened through the judicious use of bioengineering of metabolic pathways using synthetic genomics as one tool.

Finally, synthetic genomics could be applied to constructing microbes or other organisms that would act as *detectors* of toxins, chemicals, or even other (pathogenic) microbes in routine or bioterrorism surveillance. This could aid international health organizations greatly in early detection of emerging diseases.

ETHICAL AND SOCIETAL IMPLICATIONS/POLICY DISCUSSIONS ABOUT SYNTHETIC BIOLOGY

At JCVI, we consider the ethical and societal implications of the work to be as important as the scientific research. We examined ethical concerns before beginning any actual experiments or research into constructing a minimal genome or the work to construct the first synthetic cell. Here is an outline of the important work that JCVI has undertaken since 1995.

1995-1999: *Mycoplasma genitalium* and the minimal genome project

Research on the minimal genome started in 1995 after the publication of the *Mycoplasma genitalium* genome at the legacy JCVI organization, The Institute for Genomic Research (TIGR). This organism has the smallest genome of a self-replicating organism, prompting my team and me to wonder if *M. genitalium* could be a platform to determine the minimal set of genes that could still sustain cellular life. This notion and the research plan to test it underwent a thorough ethical review by a panel of experts at the University of Pennsylvania (Cho et al., Science December 1999:Vol. 286, no. 5447, pp. 2087 – 2090). The panel’s independent deliberations, published in Science along with the scientific minimal genome research, concluded that there were no strong ethical reasons that should prevent the team from continuing research in this field as long as they continued to engage in public discussions.

JCVI Work on phiX174 Synthesis: The first synthesis of a non-pathogenic virus

In 2003, before publishing the results in PNAS (“Generating a Synthetic Genome by Whole Genome Assembly: phi X174 Bacteriophage from Synthetic Oligonucleotides”), our team of scientists from JCVI contacted several Government agencies, including the US Department of

Energy (DOE), the White House Office of Science and Technology Policy (OSTP), and the National Institutes of Health, to discuss any potential repercussions of the findings. After a series of meetings (which also included Department of Homeland Security representatives) discussing the method presented in the paper, the findings were released at a press conference hosted by DOE in conjunction with the Secretary of Energy, Spencer Abraham.

JCVI Policy Team

Shortly after, in 2004, JCVI's Policy team along with the Center for Strategic & International Studies (CSIS) and the Massachusetts Institute of Technology (MIT) were funded by the Alfred P. Sloan Foundation to conduct a series of workshops and an invitational public session over a 20-month period to discuss the biosecurity and biosafety implications of synthetic genomics. Over the course of the study, the group explored the risks and benefits of the emerging technology, as well as possible safeguards to prevent abuse, such as bioterrorism. In October of 2007 the group published their findings in a report, outlining options for the field, its researchers, science administrators, and policymakers.

More recently in December of 2008, JCVI (in collaboration with social science researchers from Michigan State University and the Alberta Health Law Institute) received funding from the Alfred P. Sloan Foundation to examine ethical and societal concerns that are associated with the developing science of synthetic genomics. The ongoing research is intended to inform the scientific community as well as educate policymakers and journalists so that they may engage in informed discussions on the topic.

Ongoing Activities: Lectures, Media, Briefings for Congress and Executive Branch Officials

The JCVI team and I routinely give public lectures and presentations around the globe to both scientific and lay audiences, members of congress, schools, and other organizations. The team and I also conduct many interviews with global media (online, print, video, radio, etc.) about our work and the implications and applications.

Over the last three years the team has made several trips to Capitol Hill to brief more than 50 members of Congress. The most recent work published on the first synthetic bacterial cell published in *Science* has been reviewed by OSTP, Department of Homeland Security, the NSABB, etc. The team supports and has asked for continued review and discussion about their research.

SELECTED STUDIES OF THE SOCIETAL, ETHICAL, AND POLICY CONCERNS

To help the Committee in your deliberations, I have assembled a list of key studies of the societal, ethical, and policy concerns associated with synthetic genomics and synthetic biology.

Completed studies and reports from the United States

- Cho MK, Magnus D, Caplan AL, McGee D, and the Ethics of Genomics Group. 1999. Ethical Considerations in Synthesizing a Minimal Genome. *Science* 286: 2087-2090. <http://www.sciencemag.org/cgi/content/short/286/5447/2087>
This was the earliest study of the societal and ethical implications of synthetic genomics. Funded by an unrestricted grant from The Institute for Genomic Research Foundation (TIGR), a legacy organization of today's JCVI. The study was performed in parallel with research to define a minimal bacterial genome.
- United States Department of Energy, Office of Science, Biological and Environmental Research Advisory Committee, 2004. Synthetic Genomes: Technologies and Impact. <http://www.science.doe.gov/ober/berac/synbio.pdf>
Report of a DOE advisory group on the potential benefits and concerns associated with synthetic genomic technologies.
- National Science Advisory Board for Biosecurity (NSABB) 2006. Addressing Biosecurity Concerns Related to the Synthesis of Select Agents. http://oba.od.nih.gov/biosecurity/pdf/Final_NSABB_Report_on_Synthetic_Genomics.pdf
The Subcommittee on Synthetic Genomics of the NSABB prepared this report on security issues related to the construction of select agents using synthetic genomics technologies.
- Garfinkel MS, Endy D, Epstein GL, and Friedman RM, Synthetic Genomics: Options for Governance, 2007. <http://www.jcvi.org/cms/fileadmin/site/research/projects/synthetic-genomics-report/synthetic-genomics-report.pdf>
Report focuses on the biosecurity and biosafety concerns associated with synthetic genomics and presents and evaluates 17 policy options for consideration by policymakers. The two-year study, funded by the Alfred P. Sloan Foundation, was prepared by Michele Garfinkel and Robert Friedman, JCVI; Drew Endy, MIT; and Gerald Epstein, Center for Strategic & International Studies.
- National Academies/OECD/Royal Society, 2009. Opportunities and Challenges in the Emerging Field of Synthetic Biology: A Symposium http://sites.nationalacademies.org/PGA/stl/PGA_050738
This two-day symposium, funded by the Sloan Foundation, NSF, and BIO brought together biologists, social scientists, and policy experts to educate each other and to explore possibilities for trans-Atlantic collaborations.

Ongoing US-based studies

- Synthetic Genomics: Scientists' Understanding of Society's Concerns, Society's Understanding of the Science and Scientists

http://www.sloan.org/assets/files/press/alfred_p_sloan_foundation_funds_new_synthetic_biology_initiative_to_examine_societal_issues.pdf

JCVI's current study on the societal implications of synthetic genomics, funded by the Alfred P. Sloan Foundation (2009-2010). Garfinkel and Friedman from JCVI, in conjunction with Lori P. Knowles, University of Alberta, Health Law Institute and Paul B. Thompson, Michigan State University, Department of Philosophy, are examining the sometimes differing views of society and scientists with respect to synthetic genomics. Also examines regulatory issues in the US and the EU.

- Synthetic Biology Project: Ensuring Benefits are realized through Responsible Development <http://www.synbioproject.org/>
The Woodrow Wilson International Center for Scholars established this project as an initiative of the Foresight and Governance Program with a grant from the Alfred P. Sloan Foundation. The project aims to identify gaps in knowledge about risks, to understand public perceptions about the field, and to explore governance options to promote innovation while ensuring safety.
- Ethical Issues in Synthetic Biology: Non-Physical Moral Harms and Public Policy <http://www.thehastingscenter.org/Research/Detail.aspx?id=1548>
Funded by the Alfred P. Sloan Foundation, this project aims to identify non-physical concerns about and potential consequences of synthetic biology, including how to incorporate these concerns into public policy discussions.
- Synthetic Biology Engineering Research Center (SynBERC) <http://www.synberc.org/content/articles/human-practices>
SynBERC is a multi-institutional research group funded by National Science Foundation to explore a number of engineering issues in synthetic biology.

US Government actions

- 2009. Federal Register Notice: Department of Health and Human Services, National Institutes of Health, Office of Biotechnology Activities. Recombinant DNA Research: Proposed Actions Under the NIH Guidelines for Research Involving Recombinant DNA Molecules (NIH Guidelines). <http://oba.od.nih.gov/oba/rac/ProposeRevisionsNIHGuidelines-March-4-2009.pdf>
Considers whether synthetic DNA is identical to recombinant DNA with respect to NIH Guidelines and thus whether language in the Guidelines needs to be changed. Public comments are currently under review.
- 2009. Federal Register Notice: Department of Health and Human Services, Office of the Secretary. Screening Framework Guidance for Synthetic Double-Stranded DNA Providers. <http://www.gpo.gov/fdsys/pkg/FR-2009-11-27/pdf/E9-28328.pdf>

Provides guidance to firms that supply synthetic DNA with respect to screening orders and customers for malicious intent. Public comments are currently under review.

Completed studies and reports from the United Kingdom and Europe

- De Vriend H, for the Rathenau Institute. 2006. Constructing Life: Early social reflections on the emerging field of synthetic biology.
http://www.cisynbio.com/pdf/Constructing_Life_2006.pdf
Early and rigorous description of the constellation of societal issues that may be raised by synthetic biology.
- International Association Synthetic Biology Code, 2009. The IASB Code of Conduct for Best Practices in Gene Synthesis. http://www.ia-sb.eu/tasks/sites/synthetic-biology/assets/File/pdf/iasb_code_of_conduct_final.pdf
A suggested code of conduct for DNA synthesis firms, drafted by members of the IASB consortium. IASB is European-based; the process to draft this Code of Conduct included US firms.
- Synbiosafe (European Commission 6th Framework Program, Project on Synthetic Biology Safety and Ethical Aspects). <http://www.synbiosafe.eu/>
Three major products, all edited/directed by M. Schmidt, Synbiosafe manager: a book (Synthetic Biology: The Technoscience and Its Societal Consequences), a documentary film (SYNBIOSAFE: Safety and Ethical Aspects of Synthetic Biology), and a special issue of Systems and Synthetic Biology (Societal Aspects of Synthetic Biology)
- UK Parliamentary Office of Science and Technology, 2008. POSTnote
<http://www.parliament.uk/documents/upload/postpn298.pdf>
This document discusses possible applications and risks of new synthetic biology, including policy options for governance and development of the field.

Ongoing studies in Europe, 7th Framework program

- SYBHEL (Synthetic Biology for Human Health: Ethical and Legal Issues)
<http://sybhel.org/>
This is one of just a few ethics and policy projects worldwide to focus solely on the impacts of synthetic biology technologies with respect to human health.
- Synth-Ethics (Ethical and Regulatory Issues Raised by Synthetic Biology)
<http://www.synthethics.eu/>
This is a general project focused on safety, security, and notions of life, looking both at Europe generally and within specific countries.

Synthetic Biology Periodic Meetings: SB 1.0, 2.0, 3.0, 4.0, x.0....

The synthetic biology community holds recurring international meetings that include ethicists and social scientists with general interests in the research. Each meeting has dedicated time to presentations on societal impacts and issues.

- SB 1.0, 2005. http://syntheticbiology.org/Synthetic_Biology_1.0.html
- SB 2.0, 2006. http://webcast.berkeley.edu/event_details.php?webcastid=15766
- SB 3.0, 2007. <http://www.syntheticbiology3.ethz.ch/monday.htm>
- SB 4.0, 2008. http://sb4.biobricks.org/agenda/sb4_agenda.pdf

I thank you for the opportunity to testify before you today. I welcome any questions that you may have.

ATTACHMENTS

1. Gibson et al., 2010. Creation of a Bacterial Cell Controlled by a Chemically Synthesized Genome. Published Online May 20, 2010, Science DOI: 10.1126/science.1190719
2. Garfinkel MS, Endy D, Epstein GL, and Friedman RM, Synthetic Genomics: Options for Governance, 2007. Executive Summary
3. Company Overview: Synthetic Genomics, Inc
4. Press Release: Synthetic Genomics Inc and ExxonMobil Research and Engineering Company Sign Exclusive, Multi-Year Agreement to Develop Next Generation Biofuels Using Photosynthetic Algae

Creation of a Bacterial Cell Controlled by a Chemically Synthesized Genome

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We report the design, synthesis and assembly of the 1.08-Mbp *Mycoplasma mycoides* JCVI-syn1.0 genome starting from digitized genome sequence information and its transplantation into a *Mycoplasma capricolum* recipient cell to create new *Mycoplasma mycoides* cells that are controlled only by the synthetic chromosome. The only DNA in the cells is the designed synthetic DNA sequence, including "watermark" sequences and other designed gene deletions and polymorphisms, and mutations acquired during the building process. The new cells have expected phenotypic properties and are capable of continuous self-replication.

In 1977, Sanger and colleagues determined the complete genetic code of phage ϕ X174 (1), the first DNA genome to be completely sequenced. Eighteen years later, in 1995, our team was able to read the first complete genetic code of a self-replicating bacterium, *Haemophilus influenzae* (2). Reading the genetic code of a wide range of species has increased exponentially from these early studies. Our ability to rapidly digitize genomic information has increased by more than eight orders of magnitude over the past 25 years (3). Efforts to understand all this new genomic information have spawned numerous new computational and experimental paradigms, yet our genomic knowledge remains very limited. No single cellular system has all of its genes understood in terms of their biological roles. Even in simple bacterial cells, do the chromosomes contain the entire genetic repertoire? If so, can a complete genetic system be reproduced by chemical synthesis starting with only the digitized DNA sequence contained in a computer?

Our interest in synthesis of large DNA molecules and chromosomes grew out of our efforts over the past 15 years to build a minimal cell that contains only essential genes. This work was inaugurated in 1995 when we sequenced the genome from *Mycoplasma genitalium*, a bacterium with the smallest complement of genes of any known organism

capable of independent growth in the laboratory. More than 100 of the 485 protein-coding genes of *M. genitalium* are dispensable when disrupted one-at-a-time (4–6).

We developed a strategy for assembling viral sized pieces to produce large DNA molecules that enabled us to assemble a synthetic *M. genitalium* genome in four stages from chemically synthesized DNA cassettes averaging about 6 kb in size. This was accomplished through a combination of in vitro enzymatic methods and in vivo recombination in *Saccharomyces cerevisiae*. The whole synthetic genome (582,970 bp) was stably grown as a yeast centromeric plasmid (YCp) (7).

Several hurdles were overcome in transplanting and expressing a chemically synthesized chromosome in a recipient cell. We needed to improve methods for extracting intact chromosomes from yeast. We also needed to learn how to transplant these genomes into a recipient bacterial cell to establish a cell controlled only by a synthetic genome. Due to the fact that *M. genitalium* has an extremely slow growth rate, we turned to two faster growing mycoplasma species, *M. mycoides subspecies capri* (GM12) as donor, and *M. capricolum subspecies capricolum* (CK) as recipient.

To establish conditions and procedures for transplanting the synthetic genome out of yeast, we developed methods for cloning entire bacterial chromosomes as centromeric plasmids in yeast, including a native *M. mycoides* genome (8, 9). However, initial attempts to extract the *M. mycoides* genome from yeast and transplant it into *M. capricolum* failed. We discovered that the donor and recipient mycoplasmas share a common restriction system. The donor genome was methylated in the native *M. mycoides* cells and was therefore protected against restriction during the transplantation from a native donor cell (10). However, the bacterial genomes grown in yeast are unmethylated and so are not protected from the single restriction system of the recipient cell. We were able to overcome this restriction

barrier by methylating the donor DNA with purified methylases or crude *M. mycoides* or *M. capricolum* extracts, or by simply disrupting the recipient cell's restriction system (8).

We now have combined all of our previously established procedures and report the synthesis, assembly, cloning, and successful transplantation of the 1.08-Mbp *M. mycoides* JCVI-syn1.0 genome, to create a new cell controlled by this synthetic genome.

Results

Synthetic genome design

Design of the *M. mycoides* JCVI-syn1.0 genome was based on the highly accurate finished genome sequences of two laboratory strains of *M. mycoides* subspecies *capri* GM12 (8, 9) (11). One was the genome donor used by Lartigue et al. [GenBank accession CP001621] (10). The other was a strain created by transplantation of a genome that had been cloned and engineered in yeast, YCpMnyc1.1-*Atyellires*, [GenBank accession CP001668] (8). This project was critically dependent on the accuracy of these sequences. Although we believe that both finished *M. mycoides* genome sequences are reliable, there are 95 sites at which they differ. We began to design the synthetic genome before both sequences were finished. Consequently, most of the cassettes were designed and synthesized based upon the CP001621 sequence (11). When it was finished, we chose to use the sequence of the genome successfully transplanted from yeast (CP001668) as our design reference (except that we kept the intact *tyellires* gene). All differences that appeared biologically significant between CP001668 and previously synthesized cassettes were corrected to match it exactly (11). Sequence differences between our synthetic cassettes and CP001668 that occurred at 19 sites appeared harmless, and so were not corrected. These provide 19 polymorphic differences between our synthetic genome (JCVI-syn1.0) and the natural (non-synthetic) genome (YCpMnyc1.1) that we have cloned in yeast and use as a standard for genome transplantation from yeast (8). To further differentiate between the synthetic genome and the natural one, four watermark sequences (fig. S1) were designed to replace one or more cassettes in regions experimentally demonstrated (watermarks 1 [1246 bp] and 2 [1081 bp]) or predicted (watermarks 3 [1109 bp] and 4 [1222 bp]) to not interfere with cell viability. These watermark sequences encode unique identifiers while limiting their translation into peptides. Table S1 lists the differences between the synthetic genome and this natural standard. Figure S2 shows a map of the *M. mycoides* JCVI-syn1.0 genome. Cassette and assembly intermediate boundaries, watermarks, deletions, insertions, and genes of the *M. mycoides* JCVI syn1.0 are shown in fig. S2, and the sequence of the transplanted mycoplasma clone

sMmYCp235-1 has been submitted to GenBank (accession # CP002027).

pSynthetic genome assembly strategy

The designed cassettes were generally 1,080 bp with 80-bp overlaps to adjacent cassettes (11). They were all produced by assembly of chemically synthesized oligonucleotides by Blue Heron, Bothell, Washington. Each cassette was individually synthesized and sequence-verified by the manufacturer. To aid in the building process, DNA cassettes and assembly intermediates were designed to contain Not I restriction sites at their termini, and recombined in the presence of vector elements to allow for growth and selection in yeast (7) (11).

pA hierarchical strategy was designed to assemble the genome in 3 stages by transformation and homologous recombination in yeast from 1,078 one-kb cassettes (Fig. 1) (12, 13).

Assembly of 10-kb synthetic intermediates. In the first stage, cassettes and a vector were recombined in yeast and transferred to *E. coli* (11). Plasmid DNA was then isolated from individual *E. coli* clones and digested to screen for cells containing a vector with an assembled 10-kb insert. One successful 10-kb assembly is represented (Fig. 2a). In general, at least one 10-kb assembled fragment could be obtained by screening 10 yeast clones. However, the rate of success varied from 10-100%. All of the first-stage intermediates were sequenced. Nineteen out of 111 assemblies contained errors. Alternate clones were selected, sequence-verified, and moved on to the next assembly stage (11).

Assembly of 100-kb synthetic intermediates. The pooled 10-kb assemblies and their respective cloning vectors were transformed into yeast as above to produce 100-kb assembly intermediates (11). Our results indicated that these products cannot be stably maintained in *E. coli* so recombined DNA had to be extracted from yeast. Multiplex PCR was performed on selected yeast clones (fig. S3 and table S2). Because every 10-kb assembly intermediate was represented by a primer pair in this analysis, the presence of all amplicons would suggest an assembled 100-kb intermediate. In general, 25% or more of the clones screened contained all of the amplicons expected for a complete assembly. One of these clones was selected for further screening. Circular plasmid DNA was extracted and sized on an agarose gel alongside a supercoiled marker. Successful second-stage assemblies with the vector sequence are approximately 105 kb in length (Fig. 2b). When all amplicons were produced following multiplex PCR, a second-stage assembly intermediate of the correct size was usually produced. In some cases, however, small deletions occurred. In other instances, multiple 10-kb fragments were assembled, which produced a larger second-stage assembly intermediate. Fortunately, these differences could easily be

detected on an agarose gel prior to complete genome assembly.

Complete genome assembly. In preparation for the final stage of assembly, it was necessary to isolate microgram quantities of each of the 11 second-stage assemblies (11). As reported (14), circular plasmids the size of our second-stage assemblies could be isolated from yeast spheroplasts after an alkaline-lysis procedure. To further purify the 11 assembly intermediates, they were exonuclease-treated and passed through an anion-exchange column. A small fraction of the total plasmid DNA (1/100th) was digested with Not I and analyzed by field-inversion gel electrophoresis (FIGE) (Fig. 2c). This method produced ~1 µg of each assembly per 400 ml yeast culture (~10¹¹ cells).

The method above does not completely remove all of the linear yeast chromosomal DNA, which we found could significantly decrease the yeast transformation and assembly efficiency. To further enrich for the eleven circular assembly intermediates, ~200 ng samples of each assembly were pooled and mixed with molten agarose. As the agarose solidifies, the fibers thread through and topologically “trap” circular DNA (15). Untrapped linear DNA can then be electrophoresed out of the agarose plug, thus enriching for the trapped circular molecules. The eleven circular assembly intermediates were digested with Not I so that the inserts could be released. Subsequently, the fragments were extracted from the agarose plug, analyzed by FIGE (Fig. 2d), and transformed into yeast spheroplasts (11). In this third and final stage of assembly, an additional vector sequence was not required since the yeast cloning elements were already present in assembly 811-900.

To screen for a complete genome, multiplex PCR was carried out with 11 primer pairs, designed to span each of the eleven 100-kb assembly junctions (table S3). Of 48 colonies screened, DNA extracted from one clone (sMmYCP235) produced all 11 amplicons. PCR of the wild type (WT) positive control (YCpMmyc1.1) produced an indistinguishable set of 11 amplicons (Fig. 3a). To further demonstrate the complete assembly of a synthetic *M. mycoides* genome, intact DNA was isolated from yeast in agarose plugs and subjected to two restriction analyses; Asc I and BssH II (11). Because these restriction sites are present in three of the four watermark sequences, this choice of digestion produces restriction patterns that are distinct from the natural *M. mycoides* genome (Figs. 1 and 3b). The sMmYCP235 clone produced the restriction pattern expected for a completely assembled synthetic genome (Fig. 3c).

pSynthetic genome transplantation

Additional agarose plugs used in the gel analysis above (Fig. 3c) were also used in genome transplantation experiments (11). Intact synthetic *M. mycoides* genomes from the

sMmYCP235 yeast clone were transplanted into restriction-minus *M. capricolum* recipient cells, as described (8). Results were scored by selecting for growth of blue colonies on SP4 medium containing tetracycline and X-gal at 37 °C. Genomes isolated from this yeast clone produced 5-15 tetracycline-resistant blue colonies per agarose plug. This was comparable to the YCpMmyc1.1 control. Recovery of colonies in all transplantation experiments was dependent on the presence of both *M. capricolum* recipient cells and an *M. mycoides* genome.

Semi-synthetic genome assembly and transplantation

To aid in testing the functionality of each 100-kb synthetic segment, semi-synthetic genomes were constructed and transplanted. By mixing natural pieces with synthetic ones, the successful construction of each synthetic 100-kb assembly could be verified without having to sequence these intermediates. We cloned 11 overlapping natural 100-kb assemblies in yeast by using a previously described method (16). In 11 parallel reactions, yeast cells were co-transformed with fragmented *M. mycoides* genomic DNA (YCpMmyc1.1) that averaged ~100 kb in length and a PCR-amplified vector designed to overlap the ends of the 100-kb inserts. To maintain the appropriate overlaps so that natural and synthetic fragments could be recombined, the PCR-amplified vectors were produced via primers with the same 40-bp overlaps used to clone the 100-kb synthetic assemblies. The semi-synthetic genomes that were constructed contained between two and ten of the eleven 100-kb synthetic subassemblies (Table 1). The production of viable colonies produced after transplantation, confirmed that the synthetic fraction of each genome contained no lethal mutations. Only one of the 100-kb subassemblies, 811-900, was not viable.

Initially, an error-containing 811-820 clone was used to produce a synthetic genome that did not transplant. This was expected since the error was a single base pair deletion that creates a frameshift in *dnaA*, an essential gene for chromosomal replication. We were previously unaware of this mutation. By using a semi-synthetic genome construction strategy, we were able to pinpoint 811-900 as the source for failed synthetic transplantation experiments. Thus, we began to reassemble an error-free 811-900 assembly, which was used to produce the sMmYCP235 yeast strain. The *dnaA*-mutated genome only differs by one nucleotide from the synthetic genome in sMmYCP235. This genome served as a negative control in our transplantation experiments. The *dnaA* mutation was also repaired at the 811-900 level by genome engineering in yeast (17). A repaired 811-900 assembly was used in a final stage assembly to produce a yeast clone with a repaired genome. This yeast clone is named sMmYCP142 and could be transplanted. A complete list of genomes that

have been assembled from 11 pieces and successfully transplanted is provided in Table 1.

Characterization of the synthetic transplants

To rapidly distinguish the synthetic transplants from *M. capricolum* or natural *M. mycoides*, two analyses were performed. First, four primer pairs that are specific to each of the four watermarks were designed such that they produce four amplicons in a single multiplex PCR reaction (table S4). All four amplicons were produced by transplants generated from sMmYCp235, but not YCpMmnc1.1 (Fig. 4a). Second, the gel analysis with Asc I and BssH II, described above (Fig. 3d), was performed. The restriction pattern obtained was consistent with a transplant produced from a synthetic *M. mycoides* genome (Fig. 4b).

A single transplant originating from the sMmYCp235 synthetic genome was sequenced. We refer to this strain as *M. mycoides* JCVI-syn1.0. The sequence matched the intended design with the exception of the known polymorphisms, 8 new single nucleotide polymorphisms, an *E. coli* transposon insertion, and an 85-bp duplication (table S1). The transposon insertion exactly matches the size and sequence of IS1, a transposon in *E. coli*. It is likely that IS1 infected the 10-kb sub-assembly following its transfer to *E. coli*. The IS1 insert is flanked by direct repeats of *M. mycoides* sequence suggesting that it was inserted by a transposition mechanism. The 85-bp duplication is a result of a non-homologous end joining event, which was not detected in our sequence analysis at the 10-kb stage. These two insertions disrupt two genes that are evidently non-essential. We did not find any sequences in the synthetic genome that could be identified as belonging to *M. capricolum*. This indicates that there was a complete replacement of the *M. capricolum* genome by our synthetic genome during the transplant process.

The cells with only the synthetic genome are self replicating and capable of logarithmic growth. Scanning and transmission electron micrographs (EM) of *M. mycoides* JCVI-syn1.0 cells show small, ovoid cells surrounded by cytoplasmic membranes (Fig. 5c-5f). Proteomic analysis of *M. mycoides* JCVI-syn1.0 and the WT control (YCpMmnc1.1) by two-dimensional gel electrophoresis revealed almost identical patterns of protein spots (fig. S4) and these were clearly different from those previously reported for *M. capricolum* (10). Fourteen genes are deleted or disrupted in the *M. mycoides* JCVI-syn1.0 genome, however the rate of appearance of colonies on agar plates and the colony morphology are similar (compare Fig. 5a and b). We did observe slight differences in the growth rates in a color changing unit assay, with the JCVI-syn1.0 transplants growing slightly faster than the MmncYCp1.1 control strain (fig. S6).

Discussion

In 1995, the quality standard for sequencing was considered to be one error in 10,000 bp and the sequencing of a microbial genome required months. Today, the accuracy is substantially higher. Genome coverage of 30-50X is not unusual, and sequencing only requires a few days. However, obtaining an error-free genome that could be transplanted into a recipient cell to create a new cell controlled only by the synthetic genome was complicated and required many quality control steps. Our success was thwarted for many weeks by a single base pair deletion in the essential gene *dnaA*. One wrong base out of over one million in an essential gene rendered the genome inactive, while major genome insertions and deletions in non-essential parts of the genome had no observable impact on viability. The demonstration that our synthetic genome gives rise to transplants with the characteristics of *M. mycoides* cells implies that the DNA sequence upon which it is based is accurate enough to specify a living cell with the appropriate properties.

Our synthetic genomic approach stands in sharp contrast to a variety of other approaches to genome engineering that modify natural genomes by introducing multiple insertions, substitutions, or deletions (18-22). This work provides a proof of principle for producing cells based upon genome sequences designed in the computer. DNA sequencing of a cellular genome allows storage of the genetic instructions for life as a digital file. The synthetic genome described in this paper has only limited modifications from the naturally occurring *M. mycoides* genome. However, the approach we have developed should be applicable to the synthesis and transplantation of more novel genomes as genome design progresses (23).

We refer to such a cell controlled by a genome assembled from chemically synthesized pieces of DNA as a "synthetic cell", even though the cytoplasm of the recipient cell is not synthetic. Phenotypic effects of the recipient cytoplasm are diluted with protein turnover and as cells carrying only the transplanted genome replicate. Following transplantation and replication on a plate to form a colony (>30 divisions or >10⁹ fold dilution), progeny will not contain any protein molecules that were present in the original recipient cell (10, 24). This was previously demonstrated when we first described genome transplantation (10). The properties of the cells controlled by the assembled genome are expected to be the same as if the whole cell had been produced synthetically (the DNA software builds its own hardware).

The ability to produce synthetic cells renders it essential for researchers making synthetic DNA constructs and cells to clearly watermark their work to distinguish it from naturally occurring DNA and cells. We have watermarked the synthetic chromosome in this and our previous study (7).

If the methods described here can be generalized, design, synthesis, assembly, and transplantation of synthetic chromosomes will no longer be a barrier to the progress of synthetic biology. We expect that the cost of DNA synthesis will follow what has happened with DNA sequencing and continue to exponentially decrease. Lower synthesis costs combined with automation will enable broad applications for synthetic genomics.

We have been driving the ethical discussion concerning synthetic life from the earliest stages of this work (25, 26). As synthetic genomic applications expand, we anticipate that this work will continue to raise philosophical issues that have broad societal and ethical implications. We encourage the continued discourse.

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24. A mycoplasma cell, with a cell mass of about 10^{-13} g, contains fewer than 10^6 molecules of protein. (If it contains 20% protein this is 2×10^{-14} g protein per cell. At a molecular weight of 120 Daltons per amino acid residue each cell contains $(2 \times 10^{-14})/120 = 1.7 \times 10^{-16}$ moles of peptide residues. This is $1.7 \times 10^{-16} \times 6 \times 10^{23} = 1 \times 10^8$ residues per cell. If the average size of a protein is 300 residues then a cell contains about 3×10^5 protein molecules.) After 20 cell divisions the number of progeny exceeds the total number of protein molecules present in the recipient cell. So, following transplantation and replication to form a colony on a plate, most cells will contain no protein molecules that were present in the original recipient cell.
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28. We thank Synthetic Genomics, Inc. for generous funding of this work. We thank J. B. Hostetter, D. Radune, N. B. Fedorova, M. D. Kim, B. J. Szczypinski, I. K. Singh, J. R. Miller, S. Kaushal, R. M. Friedman, and J. Mulligan for their contributions to this work. Electron micrographs were generously provided by T. Deerinck and M. Ellisman of the National Center for Microscopy and Imaging Research at the University of California at San Diego. J.C.V. is Chief Executive Officer and Co-Chief Scientific Officer of SGI. H.O.S. is Co-Chief Scientific Officer and on the Board of Directors of SGI. C.A.H. is Chairman of the SGI Scientific Advisory Board. All three of these authors and JCVI hold SGI stock. JCVI has filed patent applications on some of the techniques described in this paper.

Supporting Online Material

www.sciencemag.org/cgi/content/full/science.1190719/DC1

Materials and Methods

Figs. S1 to S6

Tables S1 to S7

References

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Include this information when citing this paper.

Fig. 1. The assembly of a synthetic *M. mycoides* genome in yeast. A synthetic *M. mycoides* genome was assembled from 1,078 overlapping DNA cassettes in three steps. In the first step, 1,080-bp cassettes (orange arrows), produced from overlapping synthetic oligonucleotides, were recombined in sets of 10 to produce one hundred nine ~10-kb assemblies (blue arrows). These were then recombined in sets of 10 to produce eleven ~100-kb assemblies (green arrows). In the final stage of assembly, these eleven fragments were recombined into the complete genome (red circle). With the

exception of 2 constructs that were enzymatically pieced together *in vitro* (27) (white arrows), assemblies were carried out by *in vivo* homologous recombination in yeast. Major variations from the natural genome are shown as yellow circles. These include 4 watermarked regions (WM1-WM4), a 4-kb region that was intentionally deleted (94D), and elements for growth in yeast and genome transplantation. In addition, there are 20 locations with nucleotide polymorphisms (asterisks). Coordinates of the genome are relative to the first nucleotide of the natural *M. mycoides* sequence. The designed sequence is 1,077,947 bp. The locations of the Asc I and BssH II restriction sites are shown. Cassettes 1 and 800-810 were unnecessary and removed from the assembly strategy (11). Cassette 2 overlaps cassette 1104 and cassette 799 overlaps cassette 811.

Fig. 2. Analysis of the assembly intermediates. (a) Not I and Sbf I double restriction digestion analysis of assembly 341-350 purified from *E. coli*. These restriction enzymes release the vector fragments (5.5 kb and 3.4 kb) from the 10-kb insert. Insert DNA was separated from the vector DNA on a 0.8% E-gel (Invitrogen). M indicates the 1-kb DNA ladder (New England Biolabs; NEB). (b) Analysis of assembly 501-600 purified from yeast. The 105-kb circles (100-kb insert plus 5-kb vector) were separated from the linear yeast chromosomal DNA on a 1% agarose gel by applying 4.5 V/cm for 3 hours. S indicates the BAC-Tracker supercoiled DNA ladder (Epicentre). (c) Not I restriction digestion analysis of the eleven ~100-kb assemblies purified from yeast. These DNA fragments were analyzed by FICE on a 1% agarose gel. The expected insert size for each assembly is indicated. λ indicates the lambda ladder (NEB). (d) Analysis of the 11 pooled assemblies shown in (c) following topological trapping of the circular DNA and Not I digestion. One fortieth of the DNA used to transform yeast is represented.

Fig. 3. Characterization of the synthetic genome isolated from yeast. (a) Yeast clones containing a completely assembled synthetic genome were screened by multiplex PCR with a primer set that produces 11 amplicons; one at each of the 11 assembly junctions. Yeast clone sMmYCp235 (235) produced the 11 PCR products expected for a complete genome assembly. For comparison, the natural genome extracted from yeast (WT) was also analyzed. PCR products were separated on a 2% E-gel (Invitrogen). L indicates the 100-bp ladder (NEB). (b) The sizes of the expected Asc I and BssH II restriction fragments for natural (WT) and synthetic (Syn235) *M. mycoides* genomes. (c) Natural (WT) and synthetic (235) *M. mycoides* genomes were isolated from yeast in agarose plugs. In addition, DNA was purified from the host strain alone (H). Agarose plugs were digested with Asc I or BssH II and fragments were separated by clamped

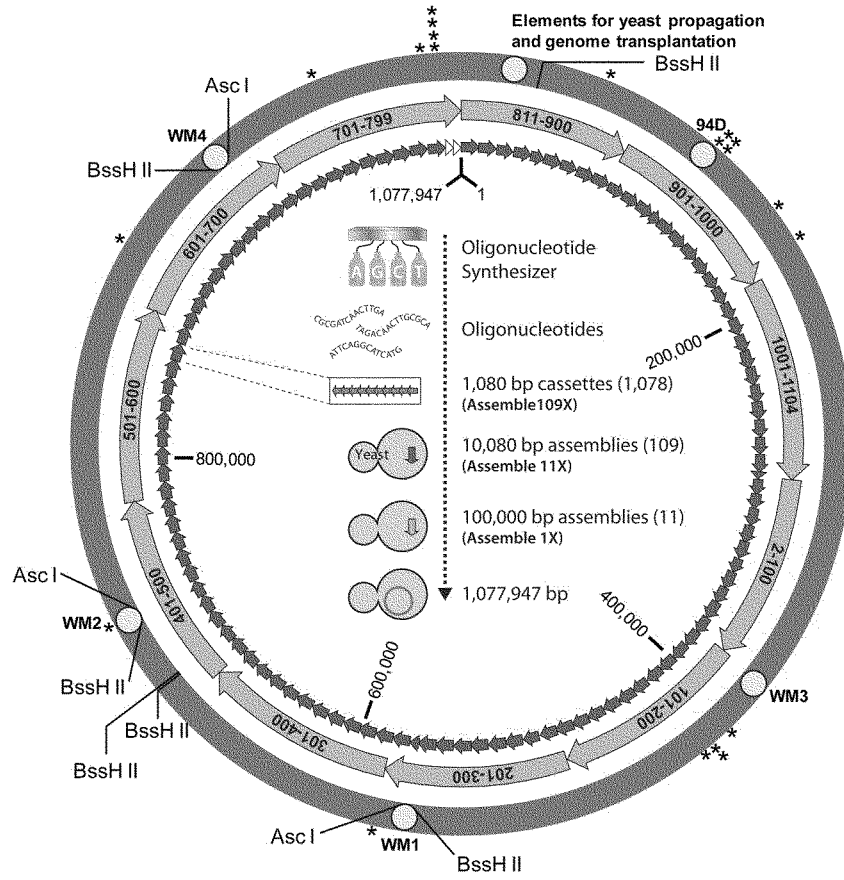
homogeneous electrical field (CHEF) gel electrophoresis. Restriction fragments corresponding to the correct sizes are indicated by the fragment numbers shown in (b).

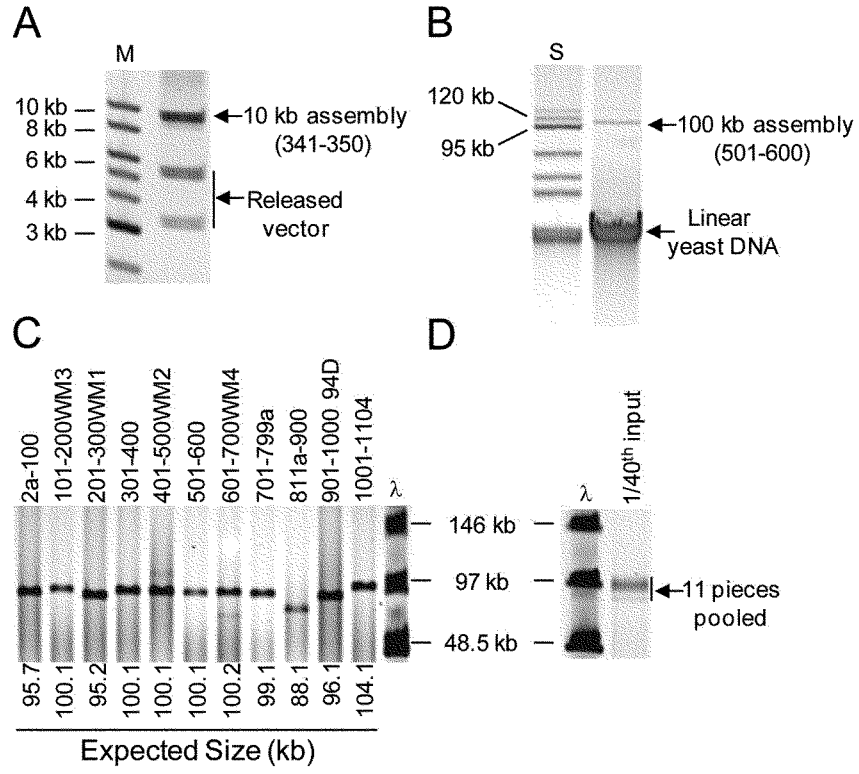
Fig. 4. Characterization of the transplants. (a) Transplants containing a synthetic genome were screened by multiplex PCR with a primer set that produces 4 amplicons; one internal to each of the four watermarks. One transplant (syn1.0) originating from yeast clone sMmYCp235 was analyzed alongside a natural, non-synthetic genome (WT) transplanted out of yeast. The transplant containing the synthetic genome produced the 4 PCR products whereas the WT genome did not produce any. PCR products were separated on a 2% E-gel (Invitrogen). (b) Natural (WT) and synthetic (syn1.0) *M. mycoides* genomes were isolated from *M. mycoides* transplants in agarose plugs. Agarose plugs were digested with Asc I or BssH II and fragments were separated by CHEF gel electrophoresis. Restriction fragments corresponding to the correct sizes are indicated by the fragment numbers shown in Fig. 3b.

Fig. 5. Images of *M. mycoides* JCVI-syn1.0 and WT *M. mycoides*. To compare the phenotype of the JCVI-syn1.0 and non-YCp WT strains, we examined colony morphology by plating cells on SP4 agar plates containing X-gal. Three days after plating, the JCVI-syn1.0 colonies are blue because the cells contain the *lacZ* gene and express beta-galactosidase, which converts the X-gal to a blue compound (a). The WT cells do not contain *lacZ* and remain white (b). Both cell types have the fried egg colony morphology characteristic of most mycoplasmas. EMs were made of the JCVI-syn1.0 isolate using two methods. (c) For scanning EM, samples were post-fixed in osmium tetroxide, dehydrated and critical point dried with CO₂, and visualized using a Hitachi SU6600 SEM at 2.0 keV. (d) Negatively stained transmission EMs of dividing cells using 1% uranyl acetate on pure carbon substrate visualized using JEOL 1200EX CTEM at 80 keV. To examine cell morphology, we compared uranyl acetate stained EMs of *M. mycoides* JCVI-syn1.0 cells (e) with EMs of WT cells made in 2006 that were stained with ammonium molybdate (f). Both cell types show the same ovoid morphology and general appearance. EMs were provided by Tom Deerinck and Mark Ellisman of the National Center for Microscopy and Imaging Research at the University of California at San Diego.

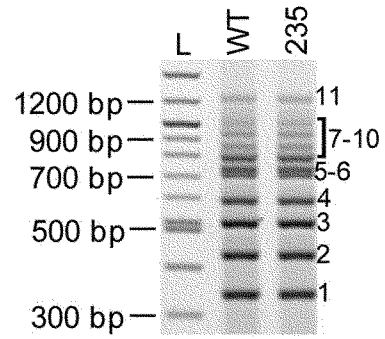
Table 1. Genomes that have been assembled from 11 pieces and successfully transplanted. Assembly 2-100 = 1, assembly 101-200 = 2, assembly 201-300 = 3, assembly 301-400 = 4, assembly 401-500 = 5, assembly 501-600 = 6, assembly 601-700 = 7, assembly 701-799 = 8, assembly 811-900 = 9, assembly 901-1000 = 10, assembly 1001-1104 = 11. WM indicates watermarked assembly.

Genome Assembly	Synthetic Fragments	Natural Fragments
Reconstituted natural genome	None	1-11
2/11 semi-synthetic genome with 1 watermark	5WM, 10	1-4, 6-9, 11
8/11 semi-synthetic genome without watermarks	1-4, 6-8, 11	5, 9, 10
9/11 semi-synthetic genome without watermarks	1-4, 6-8, 10-11	5, 9
9/11 semi-synthetic genome with 3 watermarks	1, 2WM, 3WM, 4, 6, 7WM, 8, 10-11	5, 9
10/11 semi-synthetic genome with 3 watermarks	1, 2WM, 3WM, 4, 5WM, 6, 7WM, 8, 10-11	9
11/11 synthetic genome, 811-820 correction of <i>dnaA</i>	1, 2WM, 3WM, 4, 5WM, 6, 7WM, 8, 9-11	None
11/11 synthetic genome, 811-900 correction of <i>dnaA</i>	1, 2WM, 3WM, 4, 5WM, 6, 7WM, 8, 9-11	None





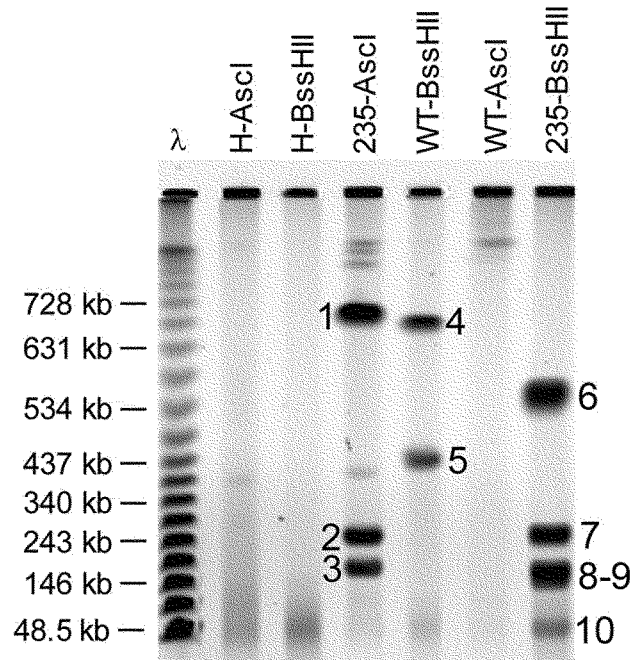
A

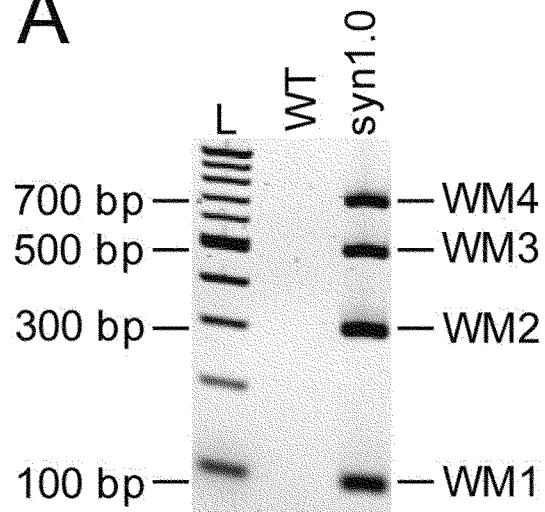
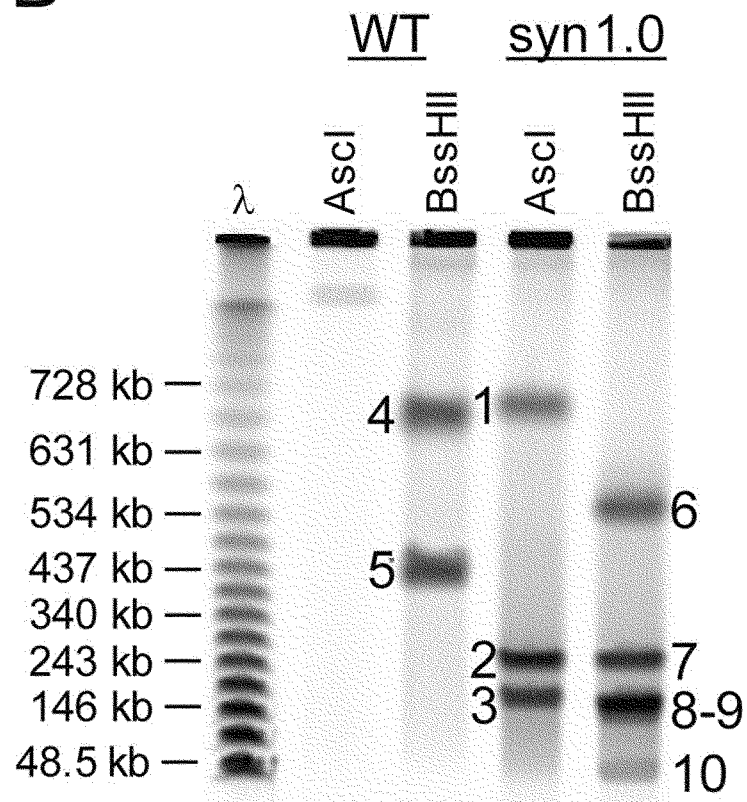


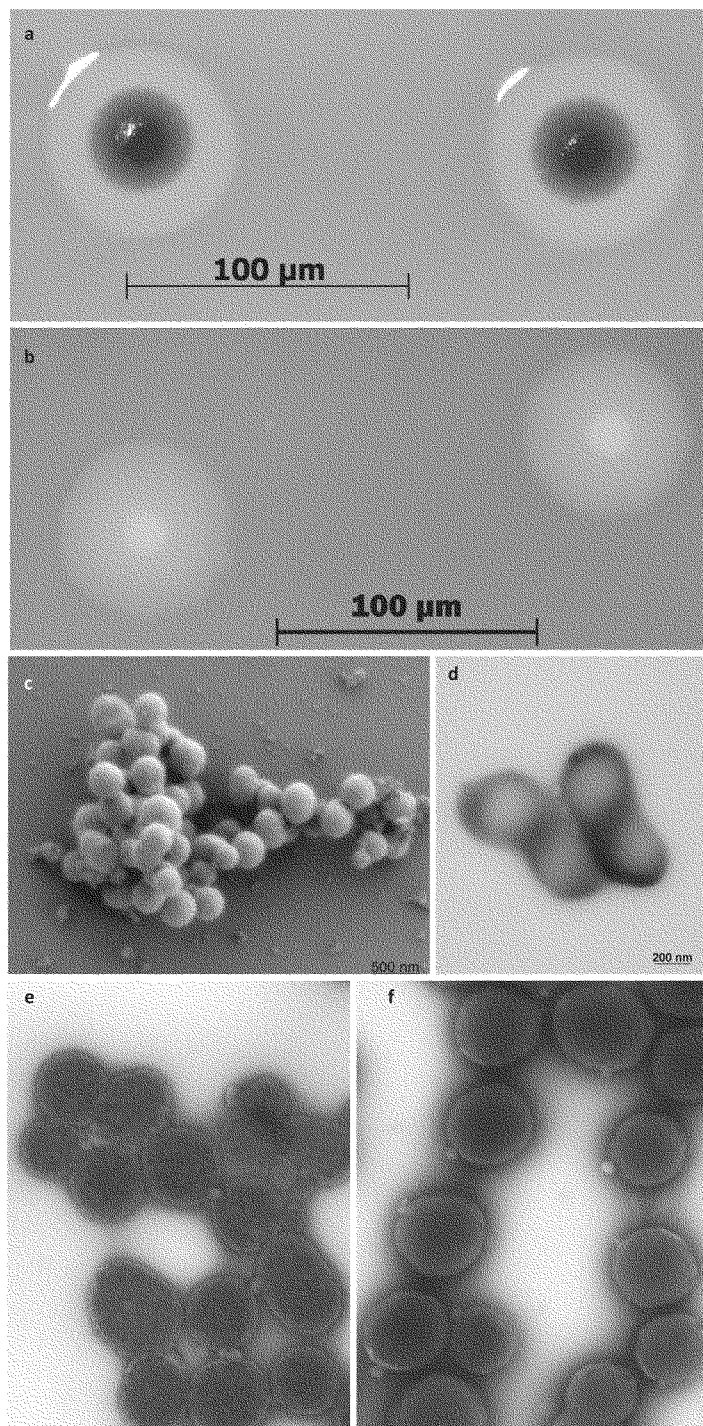
B

Strain	Digest	Fragment # and size (kb)
WT	Ascl	No sites
WT	BssHII	(4) 668 (5) 419
Syn235	Ascl	(1) 685 (2) 233 (3) 160
Syn235	BssHII	(6) 533 (7) 233 (8) 152 (9) 126 (10) 34

C



A**B**



SYNTHETIC GENOMICS | *Options for Governance*

Michele S. Garfinkel, Drew Endy, Gerald L. Epstein, and Robert M. Friedman

Gene and genome synthesis, that is, constructing long stretches of DNA from constituent chemicals, provides scientists with new and unparalleled capabilities both for understanding biology and for using it for beneficial purposes. But along with new capabilities come new risks.

Synthetic genomics combines methods for the chemical synthesis of DNA with computational techniques for its design, allowing scientists to construct genetic material that would be impossible or impractical using more conventional biotechnological approaches. The constructed DNA can then be used in a wide variety of applications that could potentially lead to improvements in human health, the environment, and basic research, among others.

The synthesis of relatively short stretches of DNA (called oligonucleotides) using specialized machines has been possible for nearly 25 years. Two advances have changed the landscape in the last five years or so. First, researchers have learned to speed up the process of stitching together small pieces of DNA into large, gene- or genome-sized pieces, so that the DNA of, for example, a medium-sized virus can be constructed in a matter of weeks. Second, there has been a proliferation of companies with proprietary technologies that are able to synthesize gene- and genome-length DNA at prices that are within reach of many researchers; these prices are rapidly dropping.

While at least some of these DNA sequences could be engineered in the laboratory using various recombinant DNA technologies, the efficiency with which arbitrary sequences of DNA can be synthesized vastly improves the speed and ease of conducting experiments and developing applications that were previously extremely difficult, or simply not possible.

The ability to quickly construct or purchase whole genes and genomes has the potential to accelerate research in a variety of areas, from high-value pharmaceuticals to biofuels to power our cars; this capability may also make it possible to respond quickly to emerging threats, such as by developing and manufacturing vaccines during a pandemic. Improvements in the speed and cost of DNA synthesis are also opening the field to new participants (e.g., engineers seeking new tools) that may transform biotechnology.

However, as in the case of many technologies, synthetic genomics may be “dual-use.” In addition to useful advances for society, it may provide those with nefarious intent new ways to harm. Although dual-use concerns exist for almost all technologies, the power and accessibility of modern biotechnology—with synthetic genomics being a prime example—makes these concerns particularly salient. Examination of the risks and benefits of this technology today has become entwined with the events of September 11, 2001 and the subsequent anthrax attacks.

This report is the result of a 20-month examination, funded by the Alfred P. Sloan Foundation, of the safety and security concerns posed by this new technology. With a core group of 14 additional people with a wide range of expertise, we undertook three tasks: assess the current state of the technology, identify potential risks and benefits to society, and formulate options for its governance.

Summary Table of Options

Does the Option:	Gene Firms				Oligo Manufacturers				DNA Synthesizers				Users and Organizations			
	A-1. Gene firm must screen orders	A-2. Bioscience officer must verify people who place orders	A-3. Physical firm must screen and bioscience officer must verify people who place orders	A-4. Firm must have information that identifies manufacturers	B-1. Characterize manufacturers	B-2. Bioscience officer must verify people who place orders	B-3. Physical firm must screen and bioscience officer must verify people who place orders	B-4. Firm must have information that identifies manufacturers	C-1. Oligo firm must screen orders	C-2. Oligo firm must screen orders	C-3. Oligo firm must screen orders	C-4. Oligo firm must screen orders	D-1. User must screen orders	D-2. User must screen orders	D-3. User must screen orders	D-4. User must screen orders
Enhance Biosecurity																
by preventing incidents?	●	●	●	○	○	○	○	○	○	○	○	○	○	○	○	○
by helping to respond?	—	—	—	○	—	—	—	○	○	○	○	○	—	—	—	—
Foster Laboratory Safety																
by preventing incidents?	○	—	○	—	○	—	○	—	—	—	—	—	●	●	○	○
by helping to respond?	—	—	—	—	—	—	—	—	—	—	—	—	●	—	—	—
Protect the Environment																
by preventing incidents?	○	—	○	—	—	—	—	—	—	—	—	—	●	●	○	○
by helping to respond?	—	—	—	○	—	—	—	○	—	—	—	—	○	●	○	—
Other Considerations:																
Minimize costs and burdens to government and industry?	○	○	○	●	○	○	○	●	●	○	○	○	○	○	○	○
Perform to potential without additional research?	○	●	●	○	○	●	○	○	●	●	○	○	○	○	○	○
Not impede research?	●	●	○	●	○	○	○	●	○	○	○	○	●	●	○	○
Promote constructive applications?	—	—	—	—	—	—	—	—	—	—	—	—	●	○	○	—

Key to Scoring:

- Most effective for this goal.
- Most effective performance on this consideration.
- Relatively effective.
- Moderately effective.
- Somewhat effective.
- Minimally effective.

Reading the evaluation diagrams

These diagrams found throughout the report allow for easy comparisons within and between options regarding their effectiveness in achieving the policy goals of biosecurity and biosafety, and their performance on other considerations.

Reading down the columns allows for an evaluation of the performance of a particular option on one goal relative to the other goals. Reading across the rows allows for comparison of the effectiveness of each option with respect to the others on any given goal or consideration. Those that perform better are indicated with circles that have more dark fill; those that perform worse have less fill.

These comparisons are qualitative: they only indicate that one option performs better or worse than another, but not by how much.

We found no “magic bullets” for assuring that synthetic genomics is used only for constructive, positive applications. We did, however, construct a series of policy interventions that could each incrementally reduce the risks from this emerging technology and, if implemented as a coordinated portfolio, could significantly reduce the risks.

We defined three major points for policy intervention:

- Commercial firms that sell synthetic DNA (oligonucleotides, genes, or genomes) to users.
- Owners of laboratory “bench-top” DNA synthesizers, with which users can produce their own DNA.
- The users (consumers) of synthetic DNA themselves and the institutions that support and oversee their work.

For each intervention point, we formulated a series of policy options. Each option was evaluated for its ability to reduce biosecurity and biosafety risks, the burden of implementation (in both resources and opportunity costs), and the degree of additional research that would be required for an option to be useful. We presented our preliminary options and analyses before a large group of subject matter experts and other stakeholders and solicited feedback that we used to revise and refine the options which are presented in their final form in this report.

The first set of options applies to firms that supply synthetic DNA, both those that supply gene- and genome-length strands of DNA and those that supply much shorter oligonucleotides. These options, treated in the report in parallel for gene-supplying firms and oligonucleotide-supplying firms are:

- I-1. Require commercial firms to use approved software for screening orders.
- I-2. People who order synthetic DNA from commercial firms must be verified as legitimate users by an Institutional Biosafety Officer or similar “responsible official.”
- I-3. Require commercial firms to use approved screening software *and* to ensure that people who place orders are verified as legitimate users by a Biosafety Officer.
- I-4. Require commercial firms to store information about customers and their orders.

The second set of options is aimed at the oversight or regulation of DNA synthesizers and the reagents used in DNA synthesis.

- II-1. Owners of DNA synthesizers must register their machines.
- II-2. Owners of DNA synthesizers must be licensed.
- II-3. A license is required both to own DNA synthesizers *and* to buy reagents and services.

Unlike the first two sets of options, which anticipate and are intended to help forestall the possibility that synthetic genomics may be misapplied by those with malicious intent, the final set of options is aimed exclusively at the legitimate users of the technology. These options cover both the education of potential users of synthetic DNA and the prior review of experiments that scientists and engineers might want to conduct:

- III-1. Incorporate education about risks and best practices as part of university curricula.
- III-2. Compile a manual for “biosafety in synthetic biology laboratories.”
- III-3. Establish a clearinghouse for best practices.
- III-4. Broaden Institutional Biosafety Committee (IBC) review responsibilities to consider risky experiments.
- III-5. Broaden IBC review responsibilities, *plus* add oversight from a national advisory group to evaluate risky experiments.
- III-6. Broaden IBC review responsibilities, *plus* enhance enforcement of compliance with biosafety guidelines.

The report presents no recommendations. A summary table of our evaluation of the various options is presented below. The options are detailed in the text of this report. To help decisionmakers choose a preferred set of options, we also include several illustrative portfolios, ranging from a modest set of controls to one that is quite aggressive. When choosing a portfolio, each policy maker will draw on his or her own values, priorities, prior beliefs, and extent of risk aversion to security and safety threats. We believe that any of the options that we include, alone or more usefully in combination, can provide a meaningful response to the threat posed by this otherwise extremely promising technology.

INSTITUTE INFORMATION

J. Craig Venter™ INSTITUTE

The **J. Craig Venter Institute (JCVI)** is a not-for-profit research institute dedicated to the advancement of the science of genomics; the understanding of its implications for society; and communication of those results to the scientific community, the public, and policymakers. Founded by J. Craig Venter, Ph.D., the JCVI is home to approximately 400 scientists and staff with expertise in human and evolutionary biology, genetics, bioinformatics/informatics, information technology, high-throughput DNA sequencing, genomic and environmental policy research, and public education in science and science policy. JCVI was formed in 2006 through the merger of several affiliated and legacy organizations—The Institute for Genomic Research (TIGR) and The Center for the Advancement of Genomics (TCAG), The J. Craig Venter Science Foundation, The Joint Technology Center, and The Institute for Biological Energy Alternatives (IBEA). The JCVI is a 501 (c)(3) organization.



Massachusetts Institute of Technology

The **Massachusetts Institute of Technology's Department of Biological Engineering** was founded in 1998 as a new MIT academic unit, with the mission of defining and establishing a new discipline fusing molecular life sciences with engineering. The goal of this biological engineering discipline is to advance fundamental understanding of how biological systems operate and to develop effective biology-based technologies for applications across a wide spectrum of societal needs including breakthroughs in diagnosis, treatment, and prevention of disease, in design of novel materials, devices, and processes, and in enhancing environmental health. The mission of MIT is to advance knowledge and educate students in science, technology, and other areas of scholarship that will best serve the nation and the world in the 21st century.

CSIS | CENTER FOR STRATEGIC & INTERNATIONAL STUDIES

The **Center for Strategic and International Studies (CSIS)** seeks to advance global security and prosperity in an era of economic and political transformation by providing strategic insights and practical policy solutions to decisionmakers. CSIS serves as a strategic planning partner for the government by conducting research and analysis and developing policy initiatives that look into the future and anticipate change. Founded in 1962 by David M. Abshire and Admiral Arleigh Burke, CSIS is a bipartisan, nonprofit organization headquartered in Washington, D.C. with more than 220 full-time staff and a large network of affiliated experts. Former U.S. senator Sam Nunn became chairman of the CSIS Board of Trustees in 1999, and John J. Hamre has led CSIS as its president and chief executive officer since April 2000.



SGI Corporate Overview

Harnessing the power of genomics, solving global challenges

Synthetic Genomics, Inc. (SGI), a privately held company founded in 2005, is developing and commercializing genomic-driven advances to sustainably meet the global demand for critical resources, beginning with energy, chemicals and high value agricultural products. The company's science could be applied towards the production of a range of products, from synthetically derived vaccines to prevent human diseases to efficient cost effective ways to produce clean drinking water. SGI is currently working in the three broad projects areas of Next Generation Fuels and Chemicals (alliance with ExxonMobil Research and Engineering Company to develop algal biofuels), Microbial-Enhanced Hydrocarbon Recovery (collaboration with BP), and Sustainable Agricultural Products (collaboration with Asiatic Centre for Genome Technology). Specifically SGI is:

- Designing metabolic pathways for the production of next generation fuels and biochemicals from a variety of feedstocks, including carbon dioxide, plant biomass and coal
- Developing new biological solutions to increase the production and/or recovery rates of subsurface hydrocarbons
- Developing high-yielding, more disease resistant and economic plant feedstocks that are supplemented with efficient and environmentally friendly microbes to replace chemical fertilizers and confer disease and stress resistance

Scientific and Business Leadership

The scientific strength of SGI lies in the decades of pioneering scientific research by its world-renowned founders, J. Craig Venter, Ph.D., Nobel Laureate Hamilton O. Smith, M.D., and the stellar scientific and business teams they have assembled. The company's scientific teams include leading researchers in plant genomics, bioinformatics, genome engineering, molecular biology, biochemistry, climate change and energy policies. In addition to the strong in-house research efforts conducted at SGI, the company sponsors fundamental research at the J. Craig Venter Institute (JCVI), a not-for-profit organization with more than 400 scientists and staff working on a variety of genomic research and policy fronts.

Science of SGI

From rapidly discovering genes and developing advances to sequence whole genomes, to making innovations in synthesizing and constructing whole chromosomes and genomes, Drs. Venter, Smith and their teams are trailblazers in the use and development of these disruptive technologies. Their ability to read and then write the genetic code led to the development of the emerging field of synthetic genomics in which genes, synthetic chromosomes and even whole genomes can be designed, synthesized and assembled from the basic chemical components of DNA. SGI is using genes as the new design components of the future to develop custom-designed modular cassettes that encode entire microbial metabolic pathways for large-scale commercial applications, including the efficient conversion of carbon dioxide, plant biomass, and coal into next generation biofuels and chemicals.



Milestones

November 2003

JCVI scientists made the first significant strides in developing a synthetic genome by assembling the 5,386 base pair genome of bacteriophage ϕ X174 (phi X).

2005

The major scientific breakthrough in synthesizing phi X was a proof of concept that gave the team assurance of the potential of this technology and encouragement to pursue this work in a commercial setting. SGI was then founded in the spring of 2005 by J. Craig Venter, Ph.D, Nobel Laureate Hamilton O. Smith, M.D., Juan Enriquez and David Kiem, M.D., J.D.

June 2007

SGI and BP formed a collaboration to develop and commercialize microbial-enhanced solutions to increase the conversion and recovery of subsurface hydrocarbons.

JCVI researchers developed genome transplantation methods and techniques used to change one bacterial species, *Mycoplasma capricolum*, into another, *Mycoplasma mycoides*.

July 2007

SGI and the Asiatic Centre for Genome Technology formed a collaboration to develop more high-yielding and disease-resistant plant feedstocks. The partnership entails sequencing oil seed plants such as oil palm and Jatropha.

January 2008

The JCVI created the first synthetic bacterial genome, *Mycoplasma genitalium* JCVI-1.0, representing the largest man-made DNA structure.

May 2008

SGI and the Asiatic Centre for Genome Technology completed the first draft assembly and annotation of the oil palm genome. The organizations also announced making progress in sequencing and analyzing the jatropha genome.

December 2008

The JCVI team made a significant advance in genome assembly in which they created the synthetic *M. genitalium* genome from 25 overlapping fragments in a one-step assembly using recombination in yeast. The team is currently working on experiments to install a fully synthetic bacterial chromosome into a recipient cell and "boot up" this synthetic chromosome.

May 2009

Jatropha genome completed.

July 2009

SGI and ExxonMobil Research and Engineering Company established a multi-year research and development strategic alliance focused on exploring the most efficient and cost effective ways to produce next generation biofuels using photosynthetic algae.

Management

J. Craig Venter, Ph.D.

Board Chairman, Co-Founder, CEO

Hamilton O. Smith, M.D.

Co-Founder, Co-Chief Scientific Officer

Aristides A.N. Patrinos, Ph.D.

President

Joel McComb

Chief Operating Officer

Chuck McBride

Chief Financial Officer

Fernanda Gandara

Vice President, Business Development

Paul Roessler, Ph.D.

Vice President, Renewable Fuels & Chemicals

Toby Richardson, Ph.D.

Vice President, Bioinformatics

Thomas Ishoey

Vice President, Subsurface Hydrocarbons

Tina Jones

Vice President, Human Resources

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Member, Scientific Advisory Board

George Poste, Ph.D.

Member, Scientific Advisory Board

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Co-Founder of SGI, Managing Director, Excel Medical Ventures

Steve Jurvetson

Managing Director of Draper Fisher Jurvetson

David Kiem, M.D., J.D.

Co-Founder of SGI, Senior Litigation Partner at Williams & Connolly

Alfonso Romo

Chairman and CEO of Plenus

Barry Schuler

Chairman and CEO of Raydiance, Inc., Managing Director of Draper Fisher Jurvetson Growth Fund

Hamilton O. Smith, M.D.

Co-Founder, Co-Chief Scientific Officer

J. Craig Venter, Ph.D.

Board Chairman, Co-Founder, CEO

Board Observers

Justin Adams

Head of Venturing - Alternative Energy, BP plc

Derrick Khoo Sin Huat

CEO of ACGT Sdn Bhd

Investors

The company's largest investors include: BP plc,

Biotechnology LLC, Draper Fisher Jurvetson,

Plenus, S.A. de C.V., ACGT Sdn Bhd, and

Meteor Group



Press Release

Synthetic Genomics Inc and ExxonMobil Research and Engineering Company Sign Exclusive, Multi-Year Agreement to Develop Next Generation Biofuels Using Photosynthetic Algae

LA JOLLA, CALIFORNIA—July 14, 2009— Synthetic Genomics Inc. (SGI), a privately held company applying genomic-driven commercial solutions to address a variety of global challenges including energy and the environment, announced today a multi-year research and development agreement with ExxonMobil Research and Engineering Company (EMRE) to develop next generation biofuels using photosynthetic algae.

As part of the multi-faceted agreement, SGI will receive milestone payments for achievements in developing biofuel products. Total funding for SGI in research and development activities and milestone payments could amount to more than \$300 million with the potential for additional income from licensing to third parties.

"This agreement between SGI and EMRE represents a comprehensive, long-term research and development exploration into the most efficient and cost effective organisms and methods to produce next generation algal biofuel," said J. Craig Venter, Founder and CEO of SGI. "We are confident that the combination of our respective expertise in science, research, engineering and scale-up should unlock the power of algae as biological energy producers in methods and scale not previously explored."

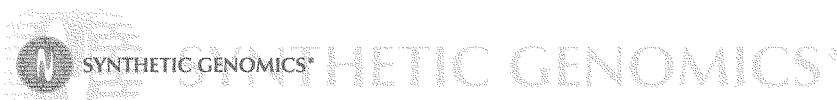
Photosynthetic algae, which include microalgae (single celled algae) and cyanobacteria (most commonly known as blue-green algae) are organisms that are very efficient at utilizing the energy from sunlight to convert carbon dioxide into cellular oils (lipids) and even some types of long-chain hydrocarbons that can be further processed into fuels and chemicals. However, naturally-occurring algae do not carry out this process at the efficiencies or rates necessary for commercial-scale production of biofuels.

Using SGI's scientific expertise and proprietary tools and technologies in genomics, metagenomics, synthetic genomics, and genome engineering as a platform, SGI and EMRE believe that biology can now be harnessed to produce sufficient quantities of biofuels.

Under the terms of the agreement, SGI will work in a systematic approach to find, optimize, and/or engineer superior strains of algae, and to define and develop the best systems for large-scale cultivation of algae and conversion of their products into useful biofuels. ExxonMobil's engineering and scientific expertise will be utilized throughout the program, from the development of systems to increase the scale of algae production through to the manufacturing of finished fuels.

-- More --

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Scientists at SGI have been working internally for several years to develop more efficient means to harvest the oils that photosynthetic algae produce. Traditionally, algae have been treated like a crop to be grown and harvested in a process that can be expensive and time consuming. One of SGI's achievements has been in engineering algal strains that produce lipids in a continuous process that is currently more efficient and cost-effective.

"This investment is an important addition to ExxonMobil's ongoing efforts to advance breakthrough technologies to help meet the world's energy challenges," said Dr. Emil Jacobs, Vice President of Research and Development at ExxonMobil Research and Engineering Company. "Meeting the world's growing energy demands will require a multitude of technologies and energy sources. We believe that biofuel produced by algae could be a meaningful part of the solution in the future because of its potential to be an economically viable, low net carbon emission transportation fuel."

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About Synthetic Genomics Inc

SGI, a privately held company founded in 2005, is dedicated to developing and commercializing genomic-driven solutions to address global energy and environment challenges. Advances in synthetic genomics present limitless applications in a variety of product areas, including: energy, chemicals and pharmaceuticals. The company's main research and business programs are currently focused on the following major bioenergy areas: designing advanced biofuels with superior properties compared to ethanol and biodiesel; harnessing photosynthetic organisms to produce value added products directly from sunlight and carbon dioxide; developing new biological solutions to increase production and/or recovery rates of subsurface hydrocarbons and developing high-yielding, more disease resistant and economic feedstocks. For more information go to www.syntheticgenomics.com

About ExxonMobil

ExxonMobil, the largest publicly traded international oil and gas company, uses technology and innovation to help meet the world's growing energy needs. ExxonMobil holds an industry-leading inventory of resources, is the largest refiner and marketer of petroleum products, and its chemical company is one of the largest in the world. For more information, visit www.exxonmobil.com

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NOTE TO EDITORS:

Dr. Emil Jacobs, vice president of research and development at ExxonMobil Research and Engineering Company, and Dr. J. Craig Venter, founder and CEO of Synthetic Genomics Inc., will be available to answer questions from media on a conference call July 14, 2009 at 10 AM ET.

Dial in details are as follows:

Date/Time: July 14, 2009, 10:00 AM ET

Participant Number: 1-888-819-8002 (Toll free)

Participant Passcode: 3031406

Mr. WAXMAN. Thank you very much, Dr. Venter. By the way, all of your statements, all your prepared statements will be in the record in their entirety and I am going to run a clock and it will turn red when the time is up. But if you are in the middle of discussing something, you can go ahead and complete your thoughts. We are not going to run strictly by the clock but it is a way of giving us guidance.

Dr. Keasling, we want to hear from you.

TESTIMONY OF JAY D. KEASLING

Mr. KEASLING. Chairman Waxman, Ranking Member Barton, and distinguished members of the committee, thank you very much for holding this hearing and for inviting me to testify.

Synthetic biology is the engineering of biology with standardized, well characterized biological components, much like we might build a computer from various components, like a hard drive, a sound card, a video card, and a power supply. Using these standardized, well characterized components, synthetic biologists are making biological engineering more reliable, easier, and less expensive than with traditional genetic engineering techniques and the resulting engineered organisms will be safer. Not only will synthetic biology enable a host of important applications to solve societal problems, it will decrease the cost of doing biological research.

Federal funding has played an important role in the development of synthetic biology. The National Science Foundation has funded the Synthetic Biology Engineering Research Center, SynBERC, which brings together many of the pioneers of synthetic biology to create new biological components, set standards for connections between these components, and demonstrate the use of these components in important applications.

SynBERC investigators are also steadyding safety, security, preparedness, and ethics around this new field of synthetic biology to ensure that these powerful technologies are used safely and wisely.

One of the most important and well-known applications of synthetic biology has been our work on engineering yeast to produce the antimalarial drug, artemisinin. There are 300 to 500 million cases of malaria at any one time, with one to three million people dying every year of the disease. Ninety percent are children under the age of five. While traditional quinine-based drugs are no longer effective, plant derived artemisinin combination therapies are highly effective but cost prohibitive for much of the world. Soon artemisinin will be in short supply, which will mean that millions of children will die needlessly. To decrease the cost and increase the supply of artemisinin, we engineered brewer's yeast to produce a precursor to the drug, by transferring into the yeast, the genes responsible for making the drug and the plant that makes it naturally. The resulting process for producing artemisinin is akin to brewing beer. The engineered yeast consumes sugar and secretes a precursor to artemisinin that can be readily converted into the drug. Through funding from the Bill and Melinda Gates Foundation, we completed the science in three years, largely due to access to well characterized biological components. The microbial production process has been licensed to Sanofi Aventis and—which will scale the process and produce the drug in the next 2 years, selling

it at cost in the developing world. We predict that this process, when fully implemented, will save a large fraction of the two million or so children who die every year from malaria. Fortuitously, artemisinin is also a hydrocarbon, which is the fundamental building block of transportation fuels.

Through advances in synthetic biology, we can reengineer this artemisinin producing yeast to produce biofuels that will work within our existing transportation infrastructure. The Joint Bio-Energy Institute in Emeryville, California, one of three DOE funded research—bioenergy research centers, is using the advances in synthetic biology to engineer microbes to transform sugars into—from cellulose and starch into hydrocarbon based biofuels that have the same quality of the fuels currently produced from petroleum. These new advanced biofuels will not require a change in our transportation infrastructure that would be necessary if ethanol were used as a pure fuel. In addition, these advanced biofuels will reduce the production of greenhouse gases, reduce our dependence on foreign oil, and could reinvigorate the U.S. agriculture economy. I am from a farm, by the way.

My research is the foundation for two California-based advanced biofuel companies that are currently employing hundreds of people and in the next 2 years, they will have fuels out on the market. Very similar technologies are being used by JBEI to engineer plants to become efficient producers of cellulose, with minimal input of water and fertilizer. Indeed, the advances in synthetic biology will allow us to have plentiful food to feed the population and biomass for fuels.

Many other applications could benefit from advances in synthetic biology, including nitrogen fixing crops that do not need ammonia-based fertilizers, microbes engineered to produce all the chemicals currently produced from petroleum, and entirely new classes as drugs to fight cancer, infections of bacteria, and a host of other diseases.

I hope that my testimony has illustrated for you the remarkable potential of synthetic biology and important role that it has to play in our Nation's research and innovative—innovation enterprise. Your actions in the support of Congress will determine whether the efforts described today are ultimately successful. This is a marathon, not a sprint, and requires consistent and continuous nurturing and case. Finally, thank you for holding this important hearing and for inviting me to participate. Please let me know if I may be of any assistance. I am happy to answer any questions at the conclusion.

[The prepared statement of Mr. Keasling follows:]

**Hearing on Developments in Synthetic Genomics and
Implications for Health and Energy**

Committee on Energy and Commerce
U.S. House of Representatives
Thursday, May 27, 2010

Testimony by Dr. Jay Keasling
University of California at Berkeley and Lawrence Berkeley National Laboratory

Chairman Waxman, Ranking Member Barton, Chairman Emeritus Dingell and distinguished members of the Committee, thank you for inviting me to testify at this important hearing. Research and scientific innovation is the key to America's long-term health and economic vitality. My scientific colleagues and I appreciate your shining a light on this new and exciting field of research and its great potential to benefit the world.

My name is Jay Keasling. I am a Professor in the Departments of Chemical Engineering and Bioengineering at the University of California at Berkeley; Acting Deputy Director of Lawrence Berkeley National Laboratory, a U.S. Department of Energy (DOE) multipurpose national laboratory operated by the University of California; Chief Executive Officer of the DOE-funded Joint BioEnergy Institute; and Director of the Synthetic Biology Engineering Research Center.

Synthetic biology is the engineering of biology to solve important problems. It is basic science with a focus on application. This emerging field of fundamental science has great potential for developing solutions to large-scale societal challenges.

Although most people are familiar with "genetic engineering" or "molecular biology," synthetic biology uses an approach and tools that differ significantly from both. The differences are in the approach and the tools utilized. For example, early molecular biologists cobbled together natural biological components and hoped that the engineered system would work. Assembling the components was challenging, and as a result, engineered organisms rarely functioned as desired. Today, synthetic biologists have improved the reliability and safety of engineered organisms by assembling standardized well-characterized components from existing well-studied organisms much like how one might assemble a computer from standard components such as a hard drive, sound card, motherboard, and power supply.

My research focuses on engineering microorganisms to produce pharmaceuticals and biofuels. In my lab, we use well-known microorganisms such as *E. coli* and yeast that

have been widely used for many years by the biotechnology industry. We introduce into these microorganisms DNA that encodes biological components such as metabolic pathways that enable the organism to transform inexpensive sugars into valuable, useful products. These products include drugs for diseases that afflict people in the developing world and carbon-neutral biofuels to reduce our dependence on foreign oil.

When I started my career in 1992 as an assistant professor at the University of California at Berkeley, biological components were relatively crude, making the engineering of microorganisms time-consuming and costly. But my colleagues and I had the idea that one could engineer microorganisms into chemical factories that produce nearly any important chemical from sugar. Unfortunately, there were few tools available to us at the time. So we began by developing tools to accurately produce a chemical of interest by controlling the expression of genes that had been transferred into cells. At that time, there was no name for what we were doing, but now it is known as synthetic biology.

Thanks to the National Science Foundation's investments in the Synthetic Biology Engineering Research Center (SynBERC), my colleagues and I are now establishing standards for the engineering of biology and creating and characterizing biological components that can be readily assembled to solve important problems. SynBERC brings together many of the pioneers (biologists and engineers from world-class institutions) of synthetic biology who are laying the foundation for the new field of synthetic biology. We are working together to construct standard, reliable, and safe building blocks that can be used in a myriad of applications. We are also studying safety, security, preparedness, and ethics issues around these powerful technologies to ensure they are used safely and wisely.

One of the most important and well-known applications of synthetic biology has been our work on engineering microorganisms to produce the anti-malarial drug artemisinin. There are 300 to 500 million cases of malaria at any one time. One to three million people die from the disease each year, and 90 percent of those are children under the age of five. While conventional quinine-based drugs are no longer effective, plant-derived artemisinin combination therapies are highly effective but cost prohibitive for much of the world.

To decrease the cost of artemisinin, we engineered a microorganism to produce a precursor chemical to the drug by transferring the genes responsible for making the drug from the plant to the microorganism. Through funding from the Bill and Melinda Gates Foundation, we completed the science in three years, largely due to ready access to well-characterized biological components. The microbial production process

has been licensed by Sanofi-Aventis, which will scale the process and produce the drug within the next two years; selling it at cost in the developing world.

The process for producing artemisinin is akin to brewing beer. The microorganism takes in a sugar and secretes a precursor to artemisinin rather than alcohol, which the yeast would produce naturally from sugar. We predict that when this process is fully implemented, the drug produced by this engineered organism could save a large fraction of the two million or so children who die every year from malaria. Launching this process in 2011 or 2012 is crucial, as the plant-derived version of the drug will soon be in short supply.

Because the engineering of biology is time-consuming and unpredictable, the artemisinin project required \$25 million in funding and roughly 50 people working on the project for the past three years. Through synthetic biology, we hope to make the engineering of biology more predictable and reliable, thereby reducing the cost to develop medicines and other useful products ranging from chemicals and fuels to consumer and commercial products.

Speaking of fuels, ethanol, which has been widely used as an oxygenate in gasoline and is the majority component of E-85, is not an ideal gasoline replacement. A gallon of ethanol packs only two-thirds of the energy of a gallon of gasoline. Ethanol is corrosive to engines and pipelines and requires energy-intensive distillation to purify. As such, its use would require significant changes to our transportation infrastructure, including replacing pipelines and automobiles at a significant cost.

Fortunately, artemisinin is a hydrocarbon, a fundamental building block for fuel. We are now re-engineering the artemisinin-producing microbes to produce drop-in biofuels. That is, through advances in synthetic biology, we can engineer these same safe, reliable, industrial microorganisms to produce biofuels that will work within our existing transportation infrastructure.

The Joint BioEnergy Institute (JBEI), a Lawrence Berkeley National Laboratory–led scientific partnership between Sandia National Laboratories, the University of California campuses at Berkeley and Davis, the Carnegie Institution for Science, and the Lawrence Livermore National Laboratory, is exploring the potential of synthetic biology to advance the development of the next generation of biofuels—liquid fuels derived from the solar energy stored in plant biomass. JBEI is one of three DOE Bioenergy Research Centers funded by the Office of Biological and Environmental Research with the Department's Office of Science.

The approach of JBEI is to use the advances in synthetic biology to engineer microorganisms to transform sugars derived from cellulosic biomass and starch into hydrocarbon-based biofuels that have the same qualities as the fuels that are currently

derived from petroleum. These new, advanced biofuels reduce the production of greenhouse gases, as they are derived from plants that use sunlight and atmospheric carbon dioxide to grow. These biofuels will reduce our dependence on foreign oil and could rejuvenate the U.S. agriculture economy, potentially making the American Midwest the new Middle East. My research is the foundation for two California-based advanced biofuel companies that are currently employing hundreds of people.

JBEI researchers have used synthetic biology and metabolic engineering techniques in *E. coli* and yeast to produce these advanced “drop-in” fuels that perform better than ethanol. The scientists are redirecting central metabolic, fatty acid, and cholesterol biosynthetic pathways to produce candidate gasoline, diesel, and jet fuel molecules. In work performed collaboratively with a Bay Area-based advanced biofuel company, my laboratory recently reported the engineering of *E. coli* to produce a biodiesel from the sugar polymer hemicellulose, a major component of plant biomass. The engineered microorganism secreted enzymes that digested hemicellulose, imported the sugar, transformed the sugar into diesel fuel, and secreted the diesel into the fermentation broth. The diesel floats to the top of the tank where the engineered *E. coli* are grown and can be skimmed off and used with very little purification. This engineering feat would not have been possible just a few years ago and certainly not without the recent advances in synthetic biology.

JBEI also has developed a new metabolic pathway that potentially could produce both advanced fuels and other molecules that might otherwise be produced from petroleum, paving the way to replace a significant portion of petroleum-based products with sugar-based products.

Very similar technologies are being used at JBEI to engineer plants to become efficient producers of cellulose with minimal input of water and fertilizer. Indeed, the advances in synthetic biology will allow us to have plentiful food to feed the population of the U.S. and the world as well as biomass for biofuels.

JBEI is also looking at the development of new and better enzymes. To break down the rugged lignocelluloses of biomass material, JBEI researchers have analyzed microbial communities in Puerto Rican rainforest soils that boast some of the planet’s highest rates of biomass degradation. To perform the analysis, scientists used the Phylochip, a credit card-sized microarray developed at Lawrence Berkeley National Laboratory that can quickly detect the presence of up to 9,000 microbial species in samples. Using bags of switchgrass as “microbe traps,” the researchers conducted a census of these soil microbes to identify the most efficient biomass-degrading bacteria and fungi. Understanding how these microbes work may provide synthetic biology solutions to more efficient and affordable deconstruction of biomass for advanced biofuels production.

Many other applications could benefit from advances in synthetic biology, including nitrogen-fixing crops that do not need ammonia-based fertilizers, microorganisms engineered to produce all of the chemicals currently produced from petroleum, and entirely new classes of drugs to fight cancer, infections of multidrug-resistant bacteria such as those that cause tuberculosis, and a host of other diseases.

I hope that my testimony has illustrated for you the remarkable potential of synthetic biology and the important role that it has to play in our nation's research and innovation enterprise. Your actions and the support of Congress will determine whether the efforts described today are ultimately successful. This is a marathon, not a sprint, and requires consistent and continuous nourishing and care.

We are very encouraged by the language adopted by the House Committee on Science and Technology regarding synthetic biology in the America COMPETES Act, and stand ready to assist Congress in any way we can as you explore and learn more about this exciting research area.

Finally, thank you, again, for holding this important hearing and for inviting me to participate. Please let me know if I may ever be of any assistance. I will be happy to answer any questions.

Mr. WAXMAN. Thank you very much for your testimony. Dr. Endy.

TESTIMONY OF DREW ENDY

Mr. ENDY. Thank you and good morning, Chairman Waxman, Ranking Member Barton, and members of the committee. In addition to my professional appointments, let me note that I serve on the Committee of Science, Technology, and Law at the National Academies, have recently been nominated to the National Science Advisory Board for Biosecurity, and was an ad hoc member of the Recombinant DNA Advisory Committee as the biosafety guidelines were recently updated to account for advances in synthetic biology and other matters.

I thought I would start by introducing some of our own work. In 2005, my lab, then at MIT, published a redesign for the genome of a virus. We did not have access to the advanced DNA and genome synthesis tools that are bringing us here today and so the students in my lab spent the entirety of a research budget, about \$200,000, struggling to build 12,000 base pairs of designer DNA, 12,000 letters. We made 600 changes to the virus genome, all at once, and we are very curious just to see if it would work.

To our great relief, the virus was capable of reproducing. Before you are alarmed, I will quickly note that the virus grew half as well as the natural isolate. That was our first experience with synthetic biology and synthetic genomics.

Also at MIT, I was involved in the development of six new courses, comprising part of what is now the new undergraduate major in biological engineering. Imagine being a teenager, matriculating at MIT, and having the possibility of becoming a biological engineer, much like you might become an electrical engineer or chemical engineer. What would you expect to learn? Well, one of the things that came out of those six courses, under Randy Rettberg's leadership, is now known as iGEM. It is the International Genetically Engineered Machines competition. This is a worldwide event. It is akin to a genetic engineering Olympics for undergraduates and so now each summer, thousands of students at hundreds of universities around the world compete and work together to build engineered genetic systems that solve problems they define. For example, we have students engineering bacteria to detect pollutants in the environment and change colors so that people might more cheaply be able to find out where problems are.

As a third example, now at Stanford, my lab is struggling to implement data storage systems inside living cells. We basically want to be able to control a small amount of information, one, two, three, or four bits, inside a yeast cell or inside a liver cell. We are not trying to replace computers. We are trying to bring computers into life so that we can act on information in places where we haven't been able to previously. For example, imagine being able to count how many times a cell has divided. That would let you study aging. It would let you begin to consider reprogramming aging. It would help to instrument cancer research and reprogram cancer or perhaps development in regenerative medicine applications.

In all of our work, we find ourselves speaking as an engineer to be very poor as engineers of biology. The genetic programs we write

tend to be 10 or 20,000 base pairs or letters of DNA law. I would have no idea how to take advantage of a million base pair fragment of synthetic DNA today and quickly program up a thousand different genes and get it to do something useful.

As it has been mentioned previously, the needs of the engineering community and the scientific community to get better at putting together the pieces of DNA and the pieces of biology to solve useful problems, will be a formidable basic research challenge for decades.

Let me turn briefly to issues of bioenergy and the national policy around bioenergy. I want to make one point quite quickly that I think is an old story and in the excitement around bioenergy, it might have been short stepped. Here is my favorite bioenergy application. In 1980, researchers figured out that you could improve laundry detergents for treating stains on clothing by using enzymes, adapted to function at cold water wash temperatures. This was an early genetic engineering project. The impact of widespread deployment of this enzyme throughout the Nation is to reduce the need for domestic hot water heating. The estimate in 1980 was the reduction in oil equivalent was about 100,000 barrels a day. One enzyme integrated upstream into our daily lives can have a net energy impact of 100,000 barrels of oil a day. I hope that is greater than the current spill in the Gulf of Mexico and if you look at biofuels as a complement to this, which are individually and independently important, 100,000 barrels of oil a day might be 100 to 200,000 acres of cropland or about 1/2000th of our cropland. So the point I would simply like to note here is as we have forward to bioenergy investments, in addition to biofuels, I would urge us to consider how future applications of biotechnology could be more directly integrated into our daily lives and upstream existence in ways that are responsible.

In the brief time I have left, let me note that I think the tools that bring us here today around genome construction raise a number of specific issues having to do with safety, security, and property rights. I will not go into those in detail here but would welcome questions on the matter. Thank you.

[The prepared statement of Mr. Endy follows:]

Testimony to the House Committee on Energy and Commerce
on Advances in Synthetic Biology and Their Potential Impact

Washington, DC
27 May 2010

Given by Drew Endy of Stanford, CA

Good Morning, Chairman Waxman, Ranking Member Barton, and Members of the Committee.

My name is Drew Endy. I am an Assistant Professor in the Department of Bioengineering at Stanford University, President of the BioBricks Foundation, and Director of the BIOFAB: International Open Facility Advancing Biotechnology (BIOFAB). I serve on the Committee on Science, Technology and Law at the National Academies and am a recent nominee to the National Science Advisory Board for Biosecurity. My own work and that of my students is the direct result of sustained public funding for basic science and engineering research from the NIH, NSF, and DOD, and for which we are grateful.

Synthetic biology has been called “extreme genetic engineering” by civil society organizations. This label is true but only in relation to the past 35 years of biotechnology that follow the invention of recombinant DNA technology and other early tools. Speaking as an engineer, the facts today suggest that we are extremely bad at engineering biology.

For example, in my own lab we are working to understand and engineer how cells make decisions, store information, and communicate. One current “holy grail” is to implement a genetically encoded 8-bit information storage system. Our deliverable is similar to a computer’s memory chip or a USB flash drive that you might use with a digital camera, except for two major differences. First, our system will only store 8 bits, which is 8 billion times less than what you could store on an electronic memory stick available today from Walmart for \$20. Second, our system is made from proteins and DNA that function inside living cells. The system works by controlling enzymes that flip DNA back and forth; a stretch of DNA pointing “left” means “0” while “right” means “1”. We will use our system to study and control cancer, aging, and development. For example, we plan to create combinatorial counters that track the number of times cells divide, and explore the possibility of building into cells additional “fail-safes” that prevent out-of-control replication, such as during cancer. Practically, the design of our first 8-bit combinatorial counter requires that we combine the DNA sequences for at least 48 genes encoding the various DNA flipping enzymes with as many more control elements. In total we need to design, build, and test about 100,000 base pairs, or letters, of highly engineered DNA. Using the best tools available it has taken us over one year to get the molecular pieces that comprise our first bit working.

The high cost and uncertainty of doing genetic engineering research has big impacts. For example, ~99% of all engineered genetic “programs” today are encoded by less than 20,000 base pairs of designer DNA. As a second example, the NIH is thought to spend ~5% of its total annual budget supporting researchers who then spend up to 50% of their time manipulating DNA by hand. Thus, while most of the attention is focused on the applications or ethics of biology and biotechnology, it is also important to look at the tools, processes, and human practices that comprise the work itself. This is where synthetic biology has a powerful role to play.

For example, we have heard today how researchers at the J. Craig Venter Institute (JCVI) reconstructed a 1 million base genome using DNA synthesis. As a related example, in 2005, researchers in Japan constructed a composite genome approaching 8 million base pairs in length, starting from natural DNA fragments. The scale of these genome construction projects is ~10 to 100-fold beyond what's required by most research projects. Very simply, today, if every publicly funded biomedical or biotechnology research team had direct access to a gene or genome printer, most researchers could focus their full attention on the challenges of understanding and applying biology to solve problems instead of spending the majority of our time "bashing" DNA.

As a second example of synthetic biology in practice, just because we have DNA printers does not mean that we will have much useful to say. We need to also discover or invent the languages and grammars that enable us to write more powerful genetic programs, moving from today's simple declarative statements – "synthesize lots of insulin" – to tomorrow's short stories and novels – "identify, attack, and destroy the tumor in this patient, and then differentiate and re-grow into healthy replacement tissue." Here is where old but powerful engineering ideas based on standardization and abstraction are starting to have an impact. For example, the public-benefit BIOFAB facility in Emeryville CA has a two-year goal of producing a first "operating system" supporting large-scale and reliable genetic programming in the bacterium *E. coli*, which is a well-studied model organism and "workhorse" of industrial biotechnology. We estimate our first cellular operating system will include ~3,000 standard biological parts encoding different cellular control functions. We intend to make this cellular operating system freely available so that all researchers can more quickly and reliably engineer useful genetic programs.

At this point, let me acknowledge that one characteristic of synthetic biology is how quickly some of the core tools continue to change. For example, over the past five years, the length of the longest genome synthesized from scratch has increased by a factor of ~100. Thus, five years from now, we might expect that further advances in synthetic biology will enable the construction of ~100 million base pair genomes, a length nearly sufficient to encode worms and flies. To be clear, the capacity to construct genomes at such scales will not mean that we know how to "weave a worm" or "fly a fly." Rather, it guarantees that we will remain challenged to become orders of magnitude better at the basic science and engineering of biology for the foreseeable future. We will also be challenged to keep pace with developments and to sustain constructive dialog and policy-making across a diversity of concerns, values, and perspectives.

Regarding the impact of synthetic biology on national energy policy generally let me make two points. First, in very rough terms, life on Earth is thought to handle 100 terawatts of energy; human civilization uses 20 terawatts. Although it might appear that biology presents us with a 5-fold surplus as a potential energy source, we depend on the energy flowing through biology to provide for many other obviously essential needs, from ecosystems to ourselves. Thus, future large-scale deployments of synthetic biology-based technologies will need to be proactively coupled to the constructive resolution of matters involving resource utilization and land use politics.

Second, from an energy perspective, the ultimate value of biology as a manufacturing platform that addresses our nation's energy needs goes beyond the production of bulk commodity products such as liquid fuels. For example, by the early 1980s, the enzymes used in laundry detergents to treat stains had been engineered to work at cold-water wash temperatures by companies such as Genencor, Inc., resulting in the potential reduction of hot water heating bills amounting to 100,000 barrels of oil per day, nationwide. Stated differently, the "energy impact" of a single engineered protein integrated upstream into our daily lives via a laundry detergent is greater than the current oil spill in the Gulf of Mexico, and is roughly equivalent to the volume of biofuel that could be produced using 1/2000th of our crop land. Synthetic biology brings us many more opportunities to better partner with biology in reducing our energy needs and net impact on the natural environment.

In closing, let me return to the work that has brought us here and briefly sketch some of its significance from a policy and governance perspective. What changes now that it is possible to construct a replicating cell from a synthesized genome?

From a safety perspective, we inherit a tradition of practical success from the genetic engineering generation. Via synthetic biology many more people will seek to work with and use biotechnology. For example, thousands of young engineering students now labor to design and synthesize simple DNA programs via the iGEM competition. We must renew and advance our understanding and teaching of best practices regarding biosafety.

From a security perspective, many people are concerned that it is now possible to directly construct harmful pathogens from DNA sequence information. This seems to me a real but remote possibility, and is likely best addressed by improvements in our capacity to respond to emerging infectious diseases, natural or otherwise, and to our public health systems. The more pressing security concern is to ensure that the tools and policies defining the future of biotechnology do not directly or inadvertently lead to a remilitarization of biology by nations.

Finally, synthetic biology advances are challenging the existing application of property rights in biotechnology. Stated plainly, as our capacity to engineer biology increases, so does the number and combinations of uses of genetic functions that will be deployed. Such novel uses and combinations are typically protected via patents. However, via synthetic biology, we are already experiencing situations in which the cost and time required to use a patent-based approach does not match the scale or pace of work. This emerging situation is likely to be exacerbated via an increased capacity to "compile" genetic material from sequences distributed via computer networks, in a fashion that should be familiar to anyone who has used or uses Napster, the Pirate Bay, or iTunes. Our capacity to explore and craft any improved ownership, sharing, and innovation frameworks underlying the future of biotechnology will have direct impacts on the development, application, and ultimate utility and acceptance of synthetic biology.

Thank you.

END OF TESTIMONY

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Mr. WAXMAN. Thank you very much. Dr. Kaebnick.

TESTIMONY OF GREGORY E. KAEBNICK

Mr. KAEBNICK. Mr. Chairman, Ranking Member Barton, and—

Mr. WAXMAN. There is a button on the base of the mic, yes.

Mr. KAEBNICK. There we go.

Mr. WAXMAN. Good.

Mr. KAEBNICK. Mr. Chairman, Ranking Member Barton, and distinguished members of the committee, thank you for inviting me here and for bringing attention to the ethical issues of this field. My name is Greg Kaebnick, I am a research scholar at The Hastings Center, nonpartisan, nonprofit, non-independent research institute that studies ethical issues in medicine and the biological sciences, editor of one of our journal, The Hastings Center Report. We are now in a 2-year project funded by the Alfred P. Sloan Foundation to investigate the ethical issues of synthetic biology.

What I want to do this morning is just to set synthetic biology within a widely used framework for we are thinking about ethics of biotechnologies and then comment very briefly on its governance.

The ethical issues fall into two broad categories. First are intrinsic concerns, as they are called, which are about whether the science is good or bad in and of itself, aside from consequences. Many people have an intrinsic objection to cloning human beings, for example. They just feel it is wrong to do full stop.

The second category involves concerns about potential consequences, risk and benefits for example. The classic intrinsic concerns about synthetic biology are that scientists are playing God, as people often say, or that life is something more than just a soup of interacting chemicals that we can see in a microscope, maybe something sacred, and scientists are overstepping their bounds in creating it.

You might worry also that synthetic biology will undermine the moral value of life, even if you don't believe that life is something more than interacting chemicals. I think beliefs about the specialness of life or the sacredness of life, for those who put it that way, are not undercut by this science. We are just talking about microbes at this point. More importantly, whatever value we do attach to microbial life, we can also find in the life of a synthesized microbe as well.

Yet another possible intrinsic objection to synthetic biology is environmentalists. We might think that it is an intrinsically undesirable intrusion into nature. Of course, even environmentalists accept that forests may sometimes be logged, so there is a question of balance here, a question of where to draw the line. If synthetic biology turned out to be beneficial to the environment, many environmentalists, myself included, would find it attractive.

Intrinsic moral concerns are important and can be important for policy, but in the case of synthetic biology as it now stands, I do not think they point the way toward regulation. I think the field should be judged and governed on the basis of the second category of moral concerns, the consequences. The field holds significant promise of benefit. There are also, however, morally serious risks. First, there are concerns about justice. Some worry that synthetic biology could be such a powerful way of making and distributing

goods, that if we aren't careful about how it is used, the benefits from it, who owns it, there could be long-term social and environmental harms.

Two other kinds of concern are about possible physical dangers. There are concerns about accidents, organisms escaping and running amuck, and about deliberate misuse. I once heard a microbiologist say that he was very enthusiastic about synthetic biology and the only thing that worries him is the possibility of catastrophe.

Synthetic biology aims at simplicity and control. One of the themes of traditional biology though is that living things usually turn out to be more complex than we thought. I believe we should guard against an overconfidence that we understand the risks of this field. We should not assume that synthetic organisms will shed the unpredictability. Inherent life tends to find a way, so might artificial life.

I would not at all call for a general moratorium on the work. I would offer some broad recommendations for how to proceed. We need, I think, first, more study of the emergence plausibility and impact of potential risks. Second, a strategy for studying the risks that brings together different disciplines and perspectives. Third, a strategy that is grounded in good science, not sheer speculation, but is flexible enough to look for the unexpected. And fourth, an analysis of whether our current regulatory framework is adequate and we should also continue the conversation about ethics.

Thank you for this opportunity to share my thoughts.

[The prepared statement of Mr. Kaebnick follows:]

Written testimony of Gregory E. Kaebnick to the House Committee on Energy and Commerce

For a hearing May 27, 2010
Delivered May 25, 2010

Mr. Chairman, Ranking Member Barton, and Distinguished Members of the Committee, thank you for inviting me to these hearings and for bringing attention to the ethical and social issues raised by this significant new field.

I am a research scholar at The Hastings Center, an independent, nonpartisan, and nonprofit research institute that has been studying ethical issues in medicine, health policy, medical research, and biotechnology since 1969. I am also editor of one of our journals, the *Hastings Center Report*. We are now in the second year of a two-year project, funded by the Alfred P. Sloan Foundation, to investigate the ethical issues of synthetic biology.

My goal this morning is chiefly to set synthetic biology within a widely accepted framework for thinking about the ethics of new technologies. I will also comment briefly on the appropriate governmental response to the field.

The ethical issues raised by synthetic biology are familiar themes in an ongoing conversation this nation has been having about biotechnologies for several decades. Moreover, I am pleased that the conversation is continuing, not only in this panel, but also with President Obama's Presidential Commission for the Study of Bioethical Issues, which will be holding hearings on synthetic biology this summer and delivering a report to the president later this year.

The concerns fall into two general categories. One has to do with whether the creation of synthetic organisms is a good or a bad thing in and of itself, aside from the consequences. These are thought of as intrinsic concerns. Many people had similar intrinsic concerns about reproductive cloning, for example; they just felt it was wrong to do, regardless of benefits. Another has to do with potential consequences—that is, with risks and benefits. The distinction between these categories can be difficult to maintain in practice, but it provides a useful organizational structure.

1. Intrinsic Concerns

I will start with the more philosophical, maybe more baffling, kind of concern—the intrinsic concerns. They are an appropriate place to start because the work just published by researchers at Synthetic Genomics, Inc., has been billed as advancing our understanding of these issues in addition to making a scientific advance.

This announcement is not the first time we have had a debate about whether biotechnology challenges deeply held views about the status of life and the power that biotechnology and medicine give us over it. There was a similar debate about gene transfer research in the 1970s and 1980s, about cloning and stem cell research in the 1990s, and—particularly in the last decade but also earlier—about various tools for enhancing human beings. They have been addressed by the President's Commission for the Study of Ethical Problems in Medicine and Biomedical and

Behavioral Research in 1983, by President Clinton's National Bioethics Advisory Council, and by President Bush's President's Council on Bioethics. These concerns are related to even older concerns in medicine about decisions to withhold or withdraw medical treatment at the end of life.

The fact that we have had this debate before speaks to its importance. I believe the intrinsic concerns deserve respect, and with some kinds of biotechnology I think they are very important, but for synthetic biology, I do not think they provide a basis for decisions about governance.

A. Religious or Metaphysical Concerns

The classic concern about synthetic biology is that it puts human beings in a role properly held by God—that scientists who do it are “playing God,” as people say. Some may also believe that life is sacred, and that scientists are violating its sacredness. Prince Charles had this in mind in a famous polemic some years ago when he lamented that biotechnology was leading to “the industrialisation of Life.”

To object to synthetic biology along these lines is to see a serious moral mistake in it. This kind of objection may be grounded in deeply held beliefs about God's goals in creating the world and the proper role of human beings within God's plan. But these views would belong to particular faiths—not everybody would share them. Moreover, there is a range of opinions even within religious traditions about what human beings may and may not do. Some people celebrate human creativity and science. They may see science as a gift from God that God intends human beings to develop and use.

The announcement that Synthetic Genomics, Inc., has created a synthetic cell appears to some to disprove the view that life is sacred, but I do not agree. Arguably, what has been created is a synthetic genome, not a completely synthetic cell. Even if scientists manage to create a fully synthetic cell, however, people who believe that life is sacred, that it is something more than interacting chemicals, could continue to defend that belief. A similar question arises about the existence of souls in cloned people: If people have souls, then surely they would have souls even if they were created in the laboratory by means of cloning techniques. By the same reasoning, if microbial life is more than a combination of chemicals, then even microbial life created in the laboratory would be more than just chemicals. In general, beliefs about the sacredness of life are not undermined by science. Moreover, even the creation of a truly synthetic cell would still start with existing materials. It would not be the kind of creating with which God is credited, which is creating something from nothing—creation *ex nihilo*.

B. Concerns that Synthetic Biology Will Undermine Morally Significant Concepts

A related but different kind of concern is that synthetic biology will simply undermine our shared understanding of important moral concepts. For example, perhaps it will lead us to think that life does not have the specialness we have often found in it, or that we humans are more powerful than we have thought in the past. This kind of concern can be expressed without talking about God's plan.

Synthetic biology need not change our understanding of the value of life, however. The fact that living things are created naturally, rather than by people, would be only one reason for seeing them as valuable, and we could continue to see them as valuable when they are created by people. Further, in its current form, synthetic biology is almost exclusively about engineering single-celled organisms, which may be less troubling to people than engineering more complex organisms. If the work is contained within the laboratory and the factory, then it might not end up broadly changing humans' views of the value of life.

Also, of course, the fact that the work challenges our ideas may not really be a moral problem. It would not be the first time that science has challenged our views of life or our place in the cosmos, and we have weathered these challenges in the past.

C. Concerns about the Human Relationship to Nature

Another way of saying that there's something intrinsically troubling about synthetic biology, again without necessarily talking about the possibility that people are treading on God's turf, is to see it as a kind of environmentalist concern. Many environmentalists want to do more than make the environment good for humans; they also want to save nature from humans—they want to save endangered species, wildernesses, "wild rivers," old-growth forests, and mountains, canyons, and caves, for example. We should approach the natural world, many feel, with a kind of reverence or gratitude, and some worry that synthetic biology—perhaps along with many other kinds of biotechnology—does not square with this value.

Of course, human beings have been altering nature throughout human history. They have been altering ecosystems, affecting the survival of species, affecting the evolution of species, and even creating new species. Most agricultural crop species, for example, are dramatically different from their ancestral forebears. The issue, then, is where to draw the line. Even people who want to preserve nature accept that there is a balance to be struck between saving trees and harvesting them for wood. There might also be a balance when it comes to biotechnology. The misgiving is that synthetic biology goes too far—it takes human control over nature to the ultimate level, where we are not merely altering existing life forms but creating new forms.

Another environmentalist perspective, however, is that synthetic biology could be developed so that it is beneficial to the environment. Synthetic Genomics, Inc. recently contracted with Exxon Mobil to engineer algae that produce gasoline in ways that not only eliminate some of the usual environmental costs of producing and transporting fuel but simultaneously absorb large amounts of carbon dioxide, thereby offsetting some of the environmental costs of burning fuel (no matter how it is produced). If that could be achieved, many who feel deeply that we should tread more lightly on the natural world might well find synthetic biology attractive. In order to achieve this benefit, however, we must be confident that synthetic organisms will not escape into the environment and cause harms there.

Concerns involving Consequences

The second category of moral concerns is about consequences—that is, risks and benefits. The promise of synthetic biology includes, for example, better ways of producing medicine,

environmentally friendlier ways of producing fuel and other substances, and remediation of past environmental damage. These are not morally trivial considerations. There are also, however, morally serious risks. These, too, fall into three categories.

Concerns about Social Justice

Synthetic biology is sometimes heralded as the start of a new industrial age. Not only will it lead to new products, but it will lead to new modes of production and distribution; instead of pumping oil out of the ground and shipping it around the world, we might be able to produce it from algae in places closer to where it will be used. Inevitably, then, it would have all sorts of large-scale economic and social consequences, some of which could be harmful and unjust. Some commentators hold, for example, that if synthetic biology generates effective ways of producing biofuels from feedstocks such as sugar cane, then farmland in poor countries would be converted from food production to sugar cane production. Another set of concerns arises over the intellectual property rights in synthetic biology. If synthetic biology is the beginning of a new industrial age, and a handful of companies received patents giving them broad control over it, the results could be unjust.

Surely we ought to avoid these consequences. It is my belief that we can do so without avoiding the technology. Also, traditional industrial methods themselves seem to be leading to disastrous long-term social consequences; if so, synthetic biology might provide a way toward better social outcomes.

Concerns about Biosafety

Another concern is about biosafety—about mechanisms for containing and controlling synthetic organisms, both during research and development and in industrial applications. The concern is that organisms will escape, turn out to have properties, at least in their new environment, different from what was intended and predicted, or maybe mutate to acquire them, and then pose a threat to public health, agriculture, or the environment. Alternatively, some of their genes might be transferred to other, wild microbes, producing wild microbes with new properties.

Controlling this risk means controlling the organisms—trying to prevent industrial or laboratory accidents, and then trying to make sure that, when organisms do escape, they are not dangerous. Many synthetic biologists argue that an organism that devotes most of its energy to producing jet fuel or medicine, that is greatly simplified (so that it lacks the genetic complexity and therefore the adaptability of a wild form), and that is designed to work in a controlled, contained environment, will simply be too weak to survive in the wild. For added assurance, perhaps engineering them with failsafe mechanisms will *ensure* that they are incapable of surviving in the wild.

Concerns about Deliberate Misuse

I once heard a well-respected microbiologist say that he was very enthusiastic about synthetic biology, and that the only thing that worries him is the possibility of catastrophe. The kind of thing that worries him is certainly possible. The 1918 flu virus has been recreated in the laboratory. In 2002, a scientist in New York stitched together stretches of nucleotides to produce a string of DNA

that was equivalent to RNA polio virus and eventually produced the RNA virus using the DNA string. More recently, the SARS virus was also created in the laboratory. Eventually, it will almost certainly be possible to recreate bacterial pathogens like smallpox. We might also be able to enhance these pathogens. Some work in Australia on mousepox suggests ways of making smallpox more potent, for example. In theory, entirely new pathogens could be created. Pathogens that target crops or livestock are also possible.

Controlling this risk means controlling the people and companies who have access to DNA synthesis or the tools they could use to synthesize DNA themselves. There are some reasons to think that the worst will never actually happen. To be wielded effectively, destructive synthetic organisms would also have to be weaponized; for example, methods must be found to disperse pathogens in forms that will lead to epidemic infection in the target population while sparing one's own population. Arguably, terrorists have better forms of attacking their enemies than with bioweapons, which are still comparatively hard to make and are very hard to control. However, our policy should amount to more than hoping for the best.

Governance

In assessing these risks and establishing oversight over synthetic biology, we do not start from square one. There is an existing framework of laws and regulations, put into action by various agencies and oversight bodies, that will apply to R&D and to different applications. The NIH is extending its guidelines for research on genetic engineering to ensure that they are applicable to research on synthetic biology. These Guidelines are enforced by the NIH's Recombinant DNA Advisory Committee and a network of Institutional Biosafety Committees at research institutions receiving federal funding. Many applications would fall under the purview of various federal laws and the agencies that enforce them. For example, a plan to release synthetic organisms into the sea to produce nutrients that would help rebuild ocean food chains would have to pass muster with the EPA. The USDA and FDA also have regulatory authority over applications. The FBI and the NIH's National Science Advisory Board for Biosecurity are formulating policy to regulate the sale of synthetic DNA sequences that might pose a threat to biosecurity.

At the same time, the current regulatory framework may need to be augmented. First, there are questions about whether the existing laws leave gaps. Research conducted by entirely privately funded laboratory might not be covered by the NIH's Guidelines, for example. Field testing of a synthetic organism—that is, release into the environment as part of basic research—might not be covered by the existing regulations of the EPA or the USDA. Questions about the adequacy of existing regulations are even more pointed when it comes to concerns about biosecurity, particularly if or when powerful benchtop synthesizers are available in every lab.

The other big question is whether the regulatory bodies' ability to do risk assessment of synthetic biology is adequate. Synthetic biology differs from older forms of genetic engineering in that a synthetic organism could combine DNA sequences found originally in many different organisms, or might even contain entirely novel genetic code. The eventual behavior of these organisms in new environments, should they accidentally end up in one, may therefore be hard to predict.

The synthetic biologists' goal of simplicity is crucial. One of the themes of traditional biology is that living things are usually more complex than they first appear. We should not assume at the outset that synthetic organisms will shed the unpredictability inherent to life. Life tends to find a way. As a starting assumption, we should expect that artificial life will try to find a way as well.

Another difficulty in assessing concerns about both biosafety and deliberate misuse is that, if the field evolves so that important and even innovative work could be done in small, private labs, even in homes, then it could be very difficult to monitor and regulate. The threats of biosafety and deliberate misuse would have to be taken yet more seriously.

Concluding Comments

I take seriously concerns that synthetic biology is bad in and of itself, and I believe that they warrant a thorough public airing, but I do not believe that they provide a good basis for restraining the technology, at least if we can be confident that the organisms will not lead to environmental damage. Better yet would be to get out in front of the technology and ensure that it benefits the environment. Possibly, some potential applications of synthetic biology are more troubling than others and should be treated differently.

Ultimately, I think the field should be assessed on its possible outcomes. At the moment, we do not understand the possible outcomes well enough. We need, I believe:

- more study of the emergence, plausibility, and impact of potential risks;
- a strategy for studying the risks that is multidisciplinary, rather than one conducted entirely within the field;
- a strategy that is grounded in good science rather than sheer speculation, yet flexible enough to look for the unexpected; and
- an analysis of whether our current regulatory framework is adequate to deal with these risks and how the framework should be augmented.

Different kinds of applications pose different risks and may call for different responses. Microbes intended for release into the environment, for example, would pose a different set of concerns than microbes designed to be kept in specialized, contained settings. Overall, however, while the risks of synthetic biology are too significant to leave the field alone, its potential benefits are too great to call for a general moratorium.

Thank you for this opportunity to share my thoughts.

Mr. WAXMAN. Thank you very much, Dr. Gaebnick. Dr. Fauci.

TESTIMONY OF ANTHONY S. FAUCI

Dr. FAUCI. Thank you, Mr. Chairman, Ranking Member Barton, members of the committee.

Mr. WAXMAN. Is your mic on?

Dr. FAUCI. Yes, it is.

Mr. WAXMAN. OK.

Dr. FAUCI. Thank you for the opportunity to discuss with you for a couple of minutes and certainly answer any questions that you would like on the role of the NIH in genome research and related research activities.

[Slide shown.]

I have here on the first visual that you could see on the screen that this is an enervative process that has been going on with NIH support in the arena of recombinant DNA technology and genomics for decades. It has everything and even things that I have recently testified before a subcommittee of this committee on, everything from the sequencing of the human genome to the sequencing of thousands of viruses and over a thousand bacteria and other microbes. Just a couple of weeks ago, we had a hearing here, shared by Mr. Pallone, Chairman Pallone, on antibiotic resistance and we spoke of the power of the tools of sequencing and recombinant DNA technology. Also, we are studying the mind microbiome, which is the flora that is contained in the human body and how it relates to both health and disease. Also, the whole arena of recombinant DNA technology, the fundamental basic and applied research that emanated from that, largely with support from the NIH, has actually resulted in a transformation of the field of the biotech industry and all of the very good things that have occurred regarding drugs and vaccines that you have already heard of, as well as a variety of other issues related to this.

[Slide shown.]

On the second visual, it is very interesting. I did a search just a couple of days ago and I just plugged into Pubmed three components, recombinant DNA, technology, genome or genomics and it turns out that almost 800,000 papers have been published on this so we are not talking about a field that was born yesterday. As you have heard from Dr. Venter, he has been working on this for decades.

[Slide shown.]

So if you go over to the next visual, I think this is important and might explain it. It is really a continuum. Synthetic biology is a continuum of a process of understanding genes and genomics that has been going on for a very long time. First, the sequencing or finding out the natural blueprint of a genome from nature. Then there was synthesis of fragments of that, genome segments or genes themselves, again, from naturally occurring blueprints, and there came the insertion of genes, either splicing out from one and putting it into another or synthesizing little fragments and putting it into a vector that can have that particular microbe or whatever do what you would like it to do, like produce insulin or human growth hormone or what have you. What you have heard today, and will hear during the question period, is the synthesis of whole

genome from a naturally occurring blueprint. The next step being, and this is going to be very, very difficult, how you can synthesize genes and genome and circuits that are really novel, that can make them de novo do what you want them to do. So it really is a continuum over many years.

I won't dwell on what was already said by several of the panelists. The extraordinary potential good applications of synthetic biology, related from everything from the environment to energy to agriculture and to the area that I and my institution are most interested in, is medicine and health. Dr. Kaebnick gave you a very nice summary of some of the ethical concerns and how he feels confident that we are on the right track here. Let me give you some specifics about that.

[Slide shown.]

If you go to this next visual here, there are a number of areas of review and oversight that really have followed along very nicely the history of the emerging field of recombinant DNA technology. When scientists first realized the power of the tools of recombinant DNA technology, they themselves did what we call self-scrutiny and self-policing. They got together and what was born of that is what we know now of the Recombinant DNA Advisory Committee or the RAC, which is housed at NIH, which sets forth the guidelines for the use of these technologies. In 2003, Dr. Venter, in a very transparent way, brought before us, we had DOE funding at the time and he came to me and others to talk about what the best approach would be, at the time that he had synthesized a virus, a much smaller microbe than what he has just done now, and out of that came the birth of what is now known as the National Science Advisory Board for BioSecurity, or NSABB, which is also housed at the NIH, which is involved in the same sort of philosophical approach as the RAC. A lot of overlap and inter-digitation there, but also concerned not only about biosafety, but about biosecurity. We can talk a bit in the question period about what is also going on about how we are going to bring into the arena of synthetic biology, the reviews and the oversights that we have had for the pre-synthetic era, namely just the sequencing and recombinant DNA technology era.

You have also heard and you mentioned in your own statement, Mr. Chairman, that President Obama, on the 20th of May, has asked his commission for the study of bioethical issues, to examine this, and within 6 months to come back to him with a report of anything that might need to be done.

[Slide shown.]

And on this last visual, I just want to tell you how I think everyone at this table thinks. What these guidelines have really established, not only for the people with government funding, in which you have some sort of a stick that you can make sure these guidelines are followed, but also it has created in the field what we call a culture of responsibility, namely to get the people involved in doing this work to realize and to understand that even when you are trying to do something good, you have got to be very careful, careful about the safety of the people that are working with you and careful about the security of what others might use in a nefarious way. So I have shown here on this, it really is a balance, the

balance of fostering and enabling scientific research and innovation with some extraordinary potential, as you have heard from the other witnesses, with making sure, according to the guidelines that I just mentioned, that we do prevent the dangerous uses of this technology.

I would be happy to answer any questions. Thank you.

[The prepared statement of Dr. Fauci follows:]



**Testimony
Before the
Committee on Energy and Commerce
United States House of Representatives**

**Advances in Synthetic Biology:
Significance and Implications**

Statement of
Anthony S. Fauci, M.D.

*Director
National Institute of Allergy and Infectious Diseases
National Institutes of Health
U.S. Department of Health and Human Services*



**For Release on Delivery
Expected at 9:00 a.m.
May 27, 2010**

Mr. Chairman and members of the Committee, thank you for the opportunity today to discuss the recent advance in synthetic biology made by Dr. J. Craig Venter and his colleagues at the J. Craig Venter Institute (JCVI), the potential practical applications of this advance, and the broader implications of synthetic biology. I am Dr. Anthony Fauci, Director of the National Institute of Allergy and Infectious Diseases (NIAID), the lead component of the National Institutes of Health (NIH), an agency of the Department of Health and Human Services (HHS), for research relating to infectious diseases, including research on the genomics of infectious microbes.

NIAID Research

NIAID supports research related to the basic understanding, treatment and prevention of infectious, immune-mediated and allergic diseases that threaten millions of human lives. NIAID-supported studies include basic research, such as microbial biology and physiology; applied research, including the development of medical diagnostics, therapeutics and vaccines; and clinical trials to evaluate experimental drugs and vaccines. We also conduct and sponsor research to understand the genomes of disease-causing microbes. A genome is the complete set of DNA (or in some cases, RNA) that contains the genes and instructions—a blueprint—for the maintenance, growth, and reproduction of an organism. Research fields such as genomics are creating a wealth of information about infectious diseases. Using advanced technologies,

researchers are developing a clearer understanding of infectious microbes, the mechanisms by which they cause disease, and the host immune responses necessary to prevent and control an infection.

NIAID has made significant investments in genomic-related activities that provide comprehensive genomic, functional genomic, bioinformatics, and proteomic resources to the scientific community for basic and applied research to rapidly address the Institute's mission and meet the public health preparedness needs of the United States and the world. NIAID-supported researchers have sequenced the complete genomes of hundreds of disease-causing organisms, defining the genetic blueprint for pathogens responsible for malaria, tuberculosis, and seasonal and pandemic influenza, among others. Data generated through NIAID-supported initiatives are rapidly made available to the research community. NIAID genomic programs not only provide the scientific community with valuable research resources, but also have enhanced NIAID research efforts in a number of areas including studies of the mechanisms by which microbes cause disease, and the development of drugs, vaccines, and diagnostics.

Although NIAID did not fund the work by the JCVI that we are discussing here today, we are supporting a number of investigators who are conducting research applying recombinant DNA technologies, genomics, and other related disciplines to study infectious diseases. Research on genomics and other advanced technologies supported by the NIH and other federal departments and

agencies—as well as private entities such as JCVI —will provide the knowledge that will allow further advances in the field of synthetic biology.

Synthetic Biology and Its Practical Applications

"Synthetic biology" can be defined a number of ways. Generally, it is considered to be the use of molecular biological techniques and chemical synthesis to mimic and even redesign natural biological systems. Advances in recombinant DNA technology and genomics, in a sense, represent the early stages along the continuum of synthetic biology and have laid the groundwork for the next frontiers of synthetic biology, which I will discuss later in my testimony.

In the early 1970s, the advent of genetic engineering using recombinant DNA technology revolutionized molecular biology. These technologies refer to techniques by which DNA molecules that code for a protein of interest are either cut out of another genome or, as technical advances occurred, are synthesized using the blueprint of a known genetic sequence. Then, by a variety of enzymatic techniques, these genetic sequences or genes are transferred into another organism. This modified organism then uses its own genetic capabilities together with the inserted gene to produce the protein of interest. These techniques of genetic engineering have been invaluable in biological and medical research, and have led to important, practical medical applications. In 1982, the Food and Drug Administration (FDA) approved the first medicine made by recombinant DNA technology—human insulin produced from a recombinant

strain of the bacteria *Escherichia coli*. In 1986, the first recombinant vaccine was approved by the FDA—a vaccine against hepatitis B virus.

As you know, last week Dr. Venter and colleagues announced that they were able to chemically synthesize the entire genome of *Mycoplasma mycoides* based on the known sequence of the microbe, replace the DNA from the bacterium *Mycoplasma capricolum* with this synthetic genome, and produce functioning bacterial cells that mimicked *M. mycoides*. This research is an important technical breakthrough in synthetic biology and our efforts to engineer and potentially synthesize novel microbes that are able to benefit humans and the environment. The potential practical applications of this advance are broad. Certainly, we hope that synthetic organisms might one day be used to create new biofuels. Organisms might be engineered to degrade waste and byproducts that are detrimental to the environment. Scientists might one day be able to create organisms that have a positive impact on agriculture and food production. And, there also are possible medical applications, including the production of biological products and vaccines.

While this is no doubt an important technical breakthrough and a leap forward for the field of synthetic biology, there is still much work to be done in this field. The researchers at JCVI took the known sequence of *M. mycoides*—its genetic blueprint—and were able to mimic it synthetically, but this effort was more complex and challenging than anticipated, occupying many talented scientists for

more than a decade at the cost tens of millions of dollars. One task ahead is the creation of a new blueprint—something that does not yet exist—that will perform the task that scientists ask it to do: sequester carbon dioxide, produce fuel, clean up waste, etc. The creation of a completely novel blueprint from scratch will be extraordinarily challenging because scientists are only beginning to understand all of the intricate circuits involved to put together such a blueprint.

Synthetic Biology and Its Broader Implications

As is the case with many of the genomic technologies that have been developed over the last several decades, synthetic biology technology potentially could be used to engineer microbes that are beneficial, but also to create microbes that may be harmful to humans and the environment. Such technologies that have both beneficial and potentially harmful applications are commonly referred to as "dual use".

While the advance made by JCVI scientists potentially could be used by those who intend to do harm, we also must recognize that this was not a simple experiment; it was an extraordinarily complex project that took many years, people, and millions of dollars to complete. While there certainly is a chance that the technology developed by JCVI researchers might be used for nefarious purposes by those with extensive resources, it is important to point out that similar, albeit simpler techniques, are in widespread usage and are an integral and vital tool in life science research and science education, including high

school through post-graduate curricula. We also must keep in mind that nature itself is already an expert at creating microbes that can cause great harm to humans. This recent advance in synthetic biology does not necessarily bring us closer to harm's way than existing technologies or nature itself.

Dual-use technologies, including synthetic biology, have been the subject of active and ongoing discussions in the scientific community for many years, and Dr. Venter and his colleagues have been active and invaluable contributors to this dialogue. This dialogue involving a substantial number of scientists has taken place in national and international scientific bodies such as the U.S. National Academy of Sciences and the Royal Society, the United Kingdom's national academy of science. Advisory bodies to the federal government, such as the NIH Recombinant DNA Advisory Committee (RAC) and the National Science Advisory Board for Biosecurity (NSABB) also have played a major role in this discourse.

The RAC was established in 1974 in response to public concerns about the safety of manipulating genetic material through the use of recombinant DNA techniques. While the membership and responsibilities of the RAC have evolved with technology over the years, it continues to serve the NIH, as well as the scientific community and lay public, as a critically important forum for open, public deliberation on the scientific, ethical, and legal issues raised by recombinant DNA technology and its basic and clinical research applications.

The RAC first issued the NIH Guidelines for Research Involving Recombinant DNA Molecules (found at http://oba.od.nih.gov/rdna/nih_guidelines_oba.html) in 1976. While compliance with the NIH Guidelines is mandatory for investigators at institutions that receive NIH funding for recombinant DNA research, the NIH Guidelines have become a universal standard for safe scientific practice in this area of research. Other federal agencies, such as U.S. Department of Agriculture, the Department of Energy, and the Department of Veterans Affairs, have made compliance with the NIH Guidelines a term and condition of their awards. The NIH Guidelines also are followed voluntarily by many companies and other institutions not otherwise subject to their requirements. At its quarterly meetings, the RAC discusses research proposals that raise novel or particularly important scientific, safety, or ethical considerations. By helping to foster awareness and understanding of these matters among scientists, the RAC has fostered a culture of responsibility among the genomic sciences community.

In addition to the RAC, NIH also manages the NSABB, which was established in 2004 to advise the Federal government on strategies to minimize the risks and harm that could result from the malevolent use of information from legitimate research, i.e., dual-use research. The NSABB advises HHS on the efficient and effective oversight of federally conducted or supported dual-use biological research, taking into consideration national security concerns and the needs of the research community. The NSABB also provides advice on the interpretation

and application of federal guidelines on dual-use research in instances where a research institution seeks additional advice.

In addition to the dual-use implications, the recent advance in synthetic biology has broadened the range of organisms that may be developed, including those with entirely novel functions. As such, this advance raises broader societal and ethical concerns about this and future advances in this field. As such, the President has directed the Presidential Commission for the Study of Bioethical Issues to undertake, as its first order of business, a study of the implications of this scientific milestone, as well as other advances that may lie ahead in this field of research. The President has asked that the Commission consult with a broad range of constituencies and provide a report of its finding and recommendations within six months.

As I have described here, the Federal government has a number of existing committees and advisory bodies that have been discussing and will continue to discuss the risks and benefits related to this advance. The President has acted swiftly to ensure that more comprehensive discussions of its implications occur outside of the scientific community. In addition, the federal government will review its existing authorities to ensure that the current legal, regulatory, and oversight framework is sufficient to mitigate the risks associated with synthetic biology.

Conclusion

As discussed above, the advance announced by Dr. Venter and his colleagues is an important step forward for the field of synthetic biology. While it is important to ensure that we proceed cautiously with this technology and protect the public against its potential misuse, we also must take care to avoid any hasty response that would harm our scientific enterprise and hamper scientific progress. It is important that we do not act rashly and place undue restrictions on our best and brightest scientists that would prevent the United States from developing and utilizing this technology effectively and responsibly for the good of mankind in addition to competing effectively with other countries who will surely adopt these techniques.

Examples of NIH-Supported Genomics and Related Research

- Sequencing of the human genome
- Sequencing of thousands of bacteria, viruses, and other microbes
- Studies of the human microbiome
- Use of recombinant DNA technology for medical interventions such as drugs and vaccines
- Other research — bioinformatics, proteomics, systems biology

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"recombinant dna" OR genomics OR genome
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1. Identification of a gene module associated with BMD through the integration of network analysis and genome-wide association data.
Farber CR

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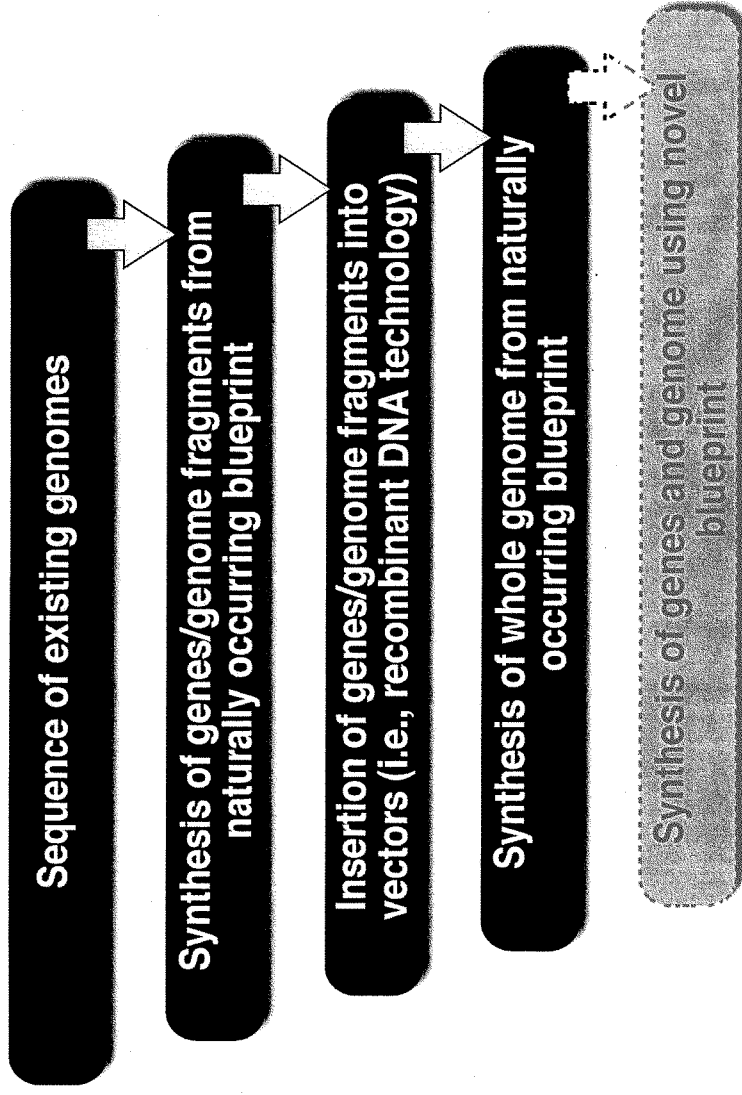
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758,811 Papers Related to Recombinant DNA Technology or Genomics in PubMed Database as of May 26, 2010

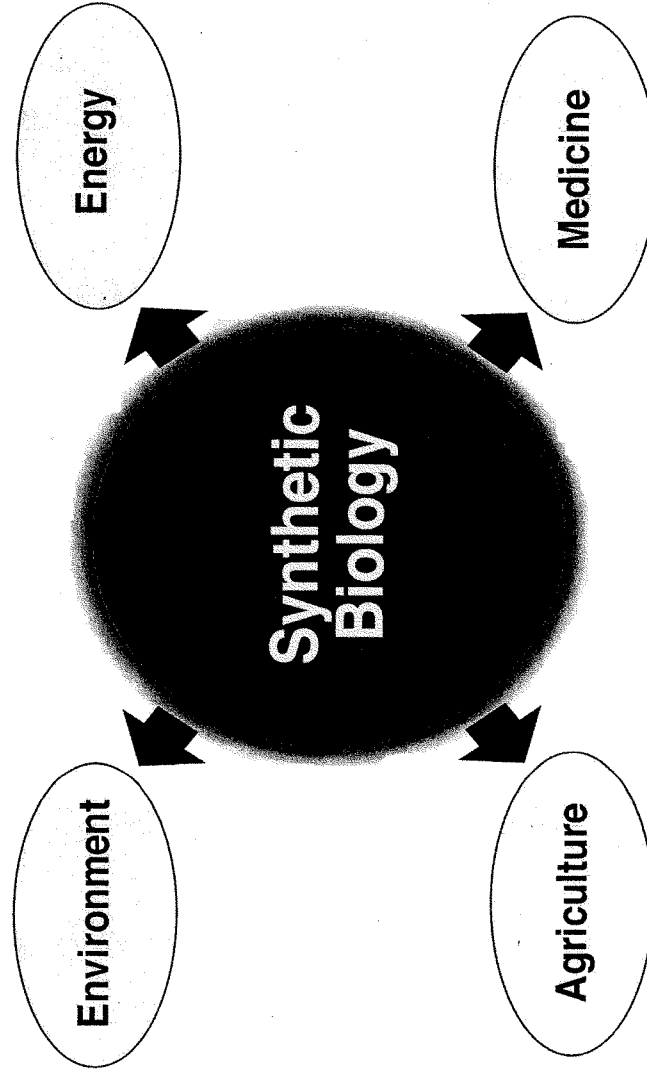
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Genomics → Synthetic Biology



Potential Applications of Synthetic Biology



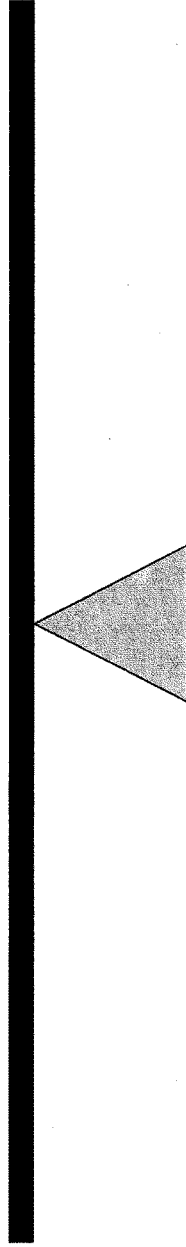
Review and Oversight

- **Recombinant DNA Advisory Committee (RAC)**
- **National Science Advisory Board for Biosecurity (NSABB)**
- **President's Commission for the Study of Bioethical Issues**
- **Others to be determined**

A Culture of Responsibility

**Fostering/
Enabling
Scientific
Research and
Innovation**

**Preventing
Dangerous
Uses of
Technology**



Mr. WAXMAN. Thank you very much for your testimony. I am going to now recognize members for 5 minute intervals to ask questions. I will start with myself.

Dr. Venter, this is a remarkable advance for science. You have described it as the software of life. I know at one point you said it was a computer created life and some of the writers about your announcement almost acted as if this is the creation of Frankenstein. Now to put it in perspective, without in any way diminishing what you achieved, the—you had to have a life to build on. You didn't develop a life from scratch. Isn't that right?

Mr. VENTER. That is absolutely correct. We, as Dr. Fauci said, we copied basically a genome of known organism. As Mr. Barton said, a goat pathogen, but we removed 14 genes that according to the scientific letter chart result of that—control its pathogenicities, so we have changed it so it is no longer a goat pathogen. But if you think about doing the very first experiment, we had to start with a control—something that would work. If we went to the bottom phase of Dr. Fauci's slide of trying to design something new, the odds are pretty low that it would have worked. Ninety-nine out of 100 of our experiments failed. Even with one error out of a million in the genetic code, we did not get life. So we copied life and we used a living cell to boot up that life. So it is, as all life on this planet, it has been life out of life. It is not new life from scratch.

Mr. WAXMAN. And as I understand it, the genome for this bacteria is about a million base pairs they use to make up strands of DNA. If we compare that with a human being, we are talking about one million to around three billion. Is that correct?

Mr. VENTER. Well, sir we have—if we count the genome components from both our parents, we have six billion letters in our genetic code. If you were looking under a microscope and you could see the human chromosomes, the piece we just made would be so small as to be invisible. So it is a gargantuan leap from what we did to anything in human beings.

Mr. WAXMAN. So people who are worried about human beings being created should relax. But meanwhile, this is a very dramatic and important step and I want to ask you more about the potential for this—for these technologies to improve health and healthcare. We are always concerned about vaccines, whether it is a vaccine for influenza or HIV. Let me just ask you about the flu vaccine first. There have been problems with using chicken eggs to make flu vaccine. It is a long, labor intensive process and the flu virus is changing and it is hard to keep up with it. Does your innovation add to the cell-based technology for influenza vaccine production and what can you project for us in the future there?

Mr. VENTER. Yes, in fact, it provides a new front end for the cell-based technology. So with these fragments that we are going to be building with NIH funding, if as we saw with H1N1, we are sequencing and tracking all these viruses, we can in 24 hours or less, with the hands of Dan Gibson sitting behind me, reconstruct new vaccine candidates that could go immediately into these cell systems for testing. So it would eliminate at least three months, possibly more. But there are other potential advantages because now we can synthesize so many different pieces. Diseases that we have not been able to get good vaccines against, such as HIV, such as

the common cold, because the virus mutates so quickly, at least the hypothetical possibility exists to make sufficient antigen components to cover a wide range in a single injection, perhaps just getting a flu shot once a decade instead of once a year.

Mr. WAXMAN. Well, HIV is a major concern and Dr. Fauci and I have been dealing with each other on that for decades now. What—tell me more about your thinking of a possible vaccine potential using this technology. How does it get us closer to accomplishing that goal?

Mr. VENTER. Well, I might defer to Dr. Fauci on that—

Mr. WAXMAN. OK.

Mr. VENTER [continuing]. He is the world's expert on HIV but I think the rapid mutation of the virus is what, from my understanding, has made it—once you make a vaccine, the virus just moves on beyond it.

Mr. WAXMAN. Dr. Fauci, you want to add anything here?

Dr. FAUCI. Yes, it is a bit more complicated with HIV, Mr. Chairman, because what Dr. Venter was describing for influenza was being able to synthesize essentially all the possible prime mutations of—you know, when we make an influenza vaccine, we make it against mostly the hemagglutinin and that is how, you know, H3N2, H2N1, H1N1, H stands for the hemagglutinin and if you are able to synthesize fragments and get, just by computational biology, you get all the possible prime mutations, you can get a head start of having those things all ready to go in a vector that you might use recombinant DNA technology to get that off the shelf more rapidly because you know what the antigen is in influenza. You don't need to synthesize a whole genome. You could just synthesize all of the possible components that you want the body to make an immune response. So it could save time when you make the initial assessment of what kind of vaccine you want and then you could just jump right into it because you already have it in the computer on the shelf. HIV is a different story because we don't even know yet what the particular protein antigen or on the envelope of that virus is that is going to induce protection. But when we do, and as you mentioned, we have testified a lot about the difficulties and that when we do, I think some of the technologies might help in being able to get an entire array of confirmations already predetermined by synthesizing them. But it is not ready for that now because we still don't know what the particular component of that virus induces the immune response that we want.

Mr. WAXMAN. OK. Thank you very much. Mr. Barton.

Mr. BARTON. Thank you, Mr. Chairman. I am not sure I am competent to ask questions in this field. It is obviously a huge intellectual challenge and a real accomplishment but the non-biologic mind of mine, I am a little bit overwhelmed by it. I will say though before I start asking questions and I kind of like the traditional way of making human beings. It is fun and it is recreational, therapeutic, and there are a lot of positives and you have these little babies that you get to let your wife raise. I mean, it is a fun thing. I am trying to understand the significance of what has transpired. Dr. Venter, what your group did, is there—you did something by create—putting things together that in and of themselves had no

life but you were able to put them together so that there was life? I mean, what is it that you have accomplished that was not accomplished before you accomplished it? What is the, in layman's terms, what has transpired that is a real leap forward?

Mr. VENTER. Well, let me first assure you we do not want to replace any of those human processes. I am a fan of them myself.

Mr. BARTON. I am—we are of like mind on that.

Mr. VENTER. So probably the best way to describe what we did, it provides a new understanding of life. When we look at these tiny microbial cells, any photographs of them, like anything we see in life, look like a fixed entity. But what is happening second to second is that genetic code is being read, making new proteins. There is turnover of these proteins. So it is a dynamic system constantly working. DNA is the software of life. If you take out the genetic code, the cell dies very quickly. That would happen to us as well. That is why radiation damage is so damaging to us. If we put in new genetic code, that cell starts reading the new genetic code, starts making new proteins and converts that cell into another species. I mean, it is the basis of life at the most dramatic level.

Mr. BARTON. Well, what did you do differently or uniquely that all these other gentlemen are patting you on the back for and saying way to go? You did——

Mr. VENTER. We started with the computer and wrote new genetic codes, starting with four bottles of chemicals. So——

Mr. BARTON. So you created that? I mean, you put together a genetic code that didn't exist in life, in the real world?

Mr. VENTER. It was largely copied off the living goat pathogen but we modified it substantially. There are 46 names written in the genetic code. It is the first species with its own Web site built into its genetic code. There are some quotations from literature and we eliminated the 14 genes associated with pathogens——

Mr. BARTON. And that had not been done before?

Mr. VENTER. That has never been done before.

Mr. BARTON. OK. And now that you have done it——

Mr. VENTER. I actually did that in the cell, converting it into a new cell. Now the only genetic code in that cell is this synthetic molecule that we made and all the proteins, all the characteristics of that cell are driven from this synthetic DNA molecule. It is self-replicating. It is a real cell. It is not an artificial cell——

Mr. BARTON. But it is a cell that did not exist before——

Mr. VENTER. That is correct.

Mr. BARTON [continuing]. The new variety.

Mr. VENTER. The new variety is a great description.

Mr. BARTON. OK. All right. Now what you did, is it proprietary? Is it patentable or is it universal knowledge that anybody can take advantage of?

Mr. VENTER. It is all of those.

Mr. BARTON. It is all of those.

Mr. VENTER. We published our paper in the Journal of Science. It is open in the scientific literature. Synthetics genomics that funded this work has also filed for patent applications on it. As you know, there has been a recent debate about whether naturally occurring DNA is patentable. All that goes back several decades to the Chakrabarty decision of the Supreme Court, saying that life

forms are patentable. This is clearly the first life form totally developed out of a computer and by humans, so it is much closer to a human invention.

Mr. BARTON. OK. Now best case, what is the best thing in a practical layman's understandable sense that could come out of what you did? If you would—a cure for cancer—could a cure for Alzheimer's, a cure for congressional ineptitude of solving the budget deficit? I mean—

Mr. VENTER. Now we are looking for miracles.

Mr. BARTON. Well, why not? Why not?

Mr. VENTER. So let me say in with the work of my colleagues, as well, I liken this to the early days of the electronics industry, where we have a number of design components and I viewed now the 40 million genes, most of which have been discovered by my institute, as design components for the future and I do not think we can imagine all the discoveries. Some of the students in Drew's classes come up with amazing little circuits out of biology. I hope in terms of our own work the immediate applications.

We are trying to do it synthetic genomics, is for example, with Exxon, see if we can capture back substantial amounts of carbon dioxide and convert it into new hydrocarbons that could go into refinery to replace taking oil out of the ground. I would be totally satisfied if that is our only accomplishment.

Mr. BARTON. I know my time has expired but I want to ask Dr. Fauci a question, if I could. What is the biggest ethical challenge from a regulatory or a moral standpoint to what Dr. Venter has discovered or accomplished?

Dr. FAUCI. Well, at this point, when you are dealing with microbes, I think the ethical challenge is probably in the field mostly of safety and security that someone does not use this technology in a nefarious manner. When you leapfrog ahead and I think that the chairman asked a question and Dr. Venter answered it appropriately, you are talking about a microbe. You are not talking about creating the human being. But for the present time, it is to make sure that the balance of benefit for humanity in the areas that I mentioned in my testimony, agriculture, medicine, energy, et cetera, clearly weigh very, very heavily down and we do all the things appropriately and in an iterative process, Mr. Barton, to look at implications and that was the reason why the President himself, in his letter of May 20, to the Commission on Bioethics said I want you to look into this and in an open, transparent discussion figure out what the implications of this might be.

Mr. BARTON. OK. Well, thank you, panel and thank you, Mr. Chairman. I do hope they discover a way to create a synthetic genome that would predispose folks to vote Republican. If they can work on that, I will support you funding that research to try that on a practical application basis. Thank you.

Mr. WAXMAN. Thank you, Mr. Barton.

Mr. Pallone.

Mr. PALLONE. Mr. Barton's comment there kind of intrigued me because I think that you cannot really program somebody to be political or not.

Mr. BARTON. You can try.

Mr. PALLONE. You can? All right. Well, whatever.

I wanted to follow up on Dr. Fauci. When you talk about the nefarious aspect of this and obviously there is some concern about that and you mentioned it in your testimony too, and of course, we think about, you know, weapons of mass destruction and you know, that type of thing. This committee oversees the select agent program at the Centers for Disease Control, which oversees the handling of many biological agents and the concern is that the genetic instructions for these agents are not themselves under the purview of this program. Nightmare scenario, for example, is if someone orders parts of DNA for a biological agent, such as smallpox from five—four to five different DNA segment manufacturers, reassembles them, and creates a weapon of mass destruction, how do we safeguard to insure that that scenario doesn't develop?

Dr. FAUCI. Thank you for that question. That is an excellent question and in anticipation of the era of synthetic biology, you know that the CDC, when someone wants to get a select agent to work with, they have to go through some very, very strict scrutiny, and as you appropriately pointed out, if people can order from a company a genome segment, not the whole organism, if they have the technological capability, they may be able to theoretically put it together, though that is really a stretch because we have Dr. Venter, who took years and years and years to do that. But in any event, if they wanted to do that, what has happened now is that the NSABB, that I mentioned to you in one of the safeguards and the areas of review and oversight, recommended to the Department of Health and Human Services to have what is called a voluntary approach on the part of the companies that make these segments. So you would get on the phone and order I would like an X-length segment of a particular sequence, that if it has to do with something that could be related to a select agent, that the person would be queried as to who you are, what your qualifications are, where you work, what you intend to do with that. To develop a consciousness of that, you don't want to be giving these segments out to anybody. That has been put in the Federal Register on November the 27th of 2009 for public comment and it is in the process now of reviewing for what particular action will be taken in that. So in anticipation of this, that has been going on.

Mr. PALLONE. Is there anything else that could be used to safeguard against, you know, that scenario other than the guidance that you mentioned? Are there any other precautions that could be taken?

Dr. FAUCI. You know, I—yes, but let me answer that question, Mr. Pallone, in a way that I think some people get a little bit confused about the balance between what can be done good and what can be done bad. Right now, microbes themselves, in their own evolutionary capacity to mutate, to change when you try and treat, to have someone manipulate, without even going near synthetic biology, the possibility of doing really bad things exists. The bad guys are not going to listen to any rules. They are going to do what they want. They do not even need this technology. So this technology has a much greater applicability to doing something really good because this type of technology doesn't exist to do—for example, you have heard of some of the things that could be done. There is not a microbe out there saying you know what I am really waiting to

do, mutate myself so I could make billions of gallons of fuel. But there are a lot of microbes that are already out there mutating, that anybody can manipulate.

Mr. PALLONE. So you are—if you know, again, I am trying to understand you as best I can, you are saying that this new technology really doesn't add much to the ability to do bad stuff. It is——

Dr. FAUCI. I——

Mr. PALLONE. That is pretty much already out there.

Dr. FAUCI. Overall, Mr. Pallone, the answer is I agree with that statement. It adds much more to what can be done in a positive sense than it pushes the envelope of what you can do in the bad sense. Because there are already enough things existing out there that if people with nefarious motives wanted to do it, they could do it. They do not need synthetic biology to do it.

Mr. PALLONE. OK. Well, that is very valuable. Thank you. Thank you, Mr. Chairman.

Mr. WAXMAN. Thank you, Mr. Pallone.

Mr. PITTS.

Mr. PITTS. Did he say me? Thank you, Mr. Chairman. Dr. Fauci, did you say there are NIH guidelines that apply to research on synthetic biology?

Dr. FAUCI. Thank you for that question. Right now, the current guidelines that emanate out of the RAC or the Recombinant DNA Advisory Committee and the NSABB do not currently involve synthetic biology. However, because of the anticipation of what we are talking about here today, the Recombinant DNA Advisory Committee put out for public comment guidelines that they are proposing would apply to synthetic biology.

Mr. PITTS. All right.

Dr. FAUCI. That has been out for public comment. The comments are in. They are being analyzed and we anticipate in June of this year that the guidelines will be revised.

Mr. PITTS. And would these guidelines apply only to institutions that accept federal funding?

Dr. FAUCI. As with the Recombinant DNA Advisory Committee, with regard to what you can do about it, mainly withdraw federal funding, the stick part of that applies to organizations that receive federal funding. But I want to reiterate what I said in my opening statement, that the guidelines of the Recombinant DNA Advisory Committee have created in institutions not only in the United States, but throughout the world, private industry or what have you, a culture of responsibility so that even though the government cannot withdraw funds, when people out there work with these technologies, it is almost unheard of to not adhere to the guidelines of the recombinant DNA technology. So over decades, it has created what we call a culture of responsibility.

Mr. PITTS. But there are no other federal biosafety guidelines that would apply to other people that use the technology?

Dr. FAUCI. There are guidelines that they use, but there is no enforcement in the sense of a private industry deciding they may want to do that. But we have now over three decades of experience of the private industry adhering very, very closely to the recombinant DNA guidelines.

Mr. PITTS. OK. Dr. Venter, now can synthetic genomes replicate, did you say?

Mr. VENTER. So the cell that I made or that our team made is self-replicated and is replicated over a billion times——

Mr. PITTS. And——

Mr. VENTER [continuing]. That is part of the definition of life.

Mr. PITTS [continuing]. Is there the potential to replicate a synthetic genome in a transplantable organ?

Mr. VENTER. I am not sure I understand the question.

Mr. PITTS. You can—you can implant this into a transplantable organ?

Mr. VENTER. The cell that we made only grows in the laboratory and in extremely rich media. This species was initially confined to goats and occasionally to sheep as sort of a commensal organism. It doesn't grow in human tissue and with the modifications we made, we don't think it will grow outside of the laboratory in any form. But we have not tested it in animals yet.

Mr. PITTS. How far away do you think we are from that scenario?

Mr. VENTER. From the scenario of microbes growing in a transplantable organ?

Mr. PITTS. Yes.

Mr. VENTER. Well, one of the studies that was published in the same issue of Science and Dr. Fauci referred to it of what we doing with the microbiome project, you have 200 trillion microbes on your body and in your body right now and you only have a 100 trillion human cells. So it is pretty hard to get any human tissue anything that is not contaminated with a wide range of microbes. We live in a microbial environment. Synthetic genomics offers nothing new there at all.

Mr. PITTS. OK. Now as far as the possible misuse of the technology was raised using to create a disease or weapon of mass destruction. What type of restraint is there in the regulatory field or out there that would prevent that? Anyone can respond.

Mr. VENTER. I will defer to Dr. Fauci or somebody else.

Dr. FAUCI. Yes, thank you for that question. I actually went over it but I would happy to briefly review it.

There are guidelines for anyone who receives federal funding that need to be adhered to from both a biosafety and most recently, with the new boards that we have for biosecurity and bio-assurity. The guidelines themselves are enforceable by the withdrawal of federal funding. However, it has been our uniform experience, that even those organizations that do not take any federal funding, when they do work in the area of recombinant DNA technology, and remember this synthetic biology that we are talking about today is not a technique that is out there for everyone to use. It took Dr. Venter many, many years to get to the point where we are today is that even if you stick just with recombinant DNA technology, that even those who don't have the federal funding have over the decades uniformly adhered to those guidelines.

If you talk about bad people wanting to do bad things, guidelines don't stop them. So if someone wants to use the technology that is available widely to try and engineer a microbe to be resistant to a particular drug, they are going to do that in a nefarious, secretive way that a guideline would not at all have anything—any deter-

rence on that. So the issue that we try to do is to make sure that since these technologies can do so much good, to make sure that people don't inadvertently, mistakenly, accidentally do something bad and that is what the guidelines are for, for the people with the expertise with the people who are trying to do very good things with them don't inadvertently hurt themselves, others, or create something that they wish they did not create. But when you are talking about what kinds of—beyond guidelines, what kind of enforcement do we have, the people who are going to break that are not going to be out there publicly looking to be enforced. It is going to be in a manner that is nefarious and secretive.

Mr. WAXMAN. Thank you, Mr. Pitts.

Mr. PITTS. Thank you.

Mr. WAXMAN. Ms. Eshoo.

Ms. ESHOO. Mr. Chairman, thank you for holding this hearing. We go to many hearings and some have a feeling of drudgery to them and there are other adjectives that one—that come to mind. This is really stunning and I am very, very grateful to each one of you for being here today and what you are doing is extraordinary. Thank you, Dr. Endy, for coming. Dr. Endy is, as he said, is from Stanford University, which I am so proud to represent. Lawrence Livermore is here. You really represent, I think, the genius of the country in this area and Dr. Fauci, you always honor us with your presence and your knowledge. I can't help but think that in the 20th century that it was marked by the advances that we made in the physical sciences and that what you are presenting here today is that the 21st century that America will be known or can be known for the mark that we will make in the life sciences. So I thank you for the work that you are doing. I think it is stunning. I think it is hopeful and as I try to bring together, you know, the whole issue of synthetic biology, in many ways, it is a description of what goes on in my district because it is a combination of the engineering of the high technology and the biology and again, I think it is not only stunning, I think it is exciting. What I would like to learn from you are what—how far off some of the practical applications of this—of synthetic biology is. The committee has spent some time, of course, we were—spent a lot of time on H1N1 and how it would be handled and the whole issue of—you know, the problems of using chicken eggs and the time that, you know, that the process is long and labor intensive. So we worked hard to ensure the development of the cell-based alternatives that would then be used to reduce production time by weeks. So Dr. Venter, I would like to know from you or maybe you can help us by answering the following question. How does your innovation add to these cell-based technologies for influenza vaccine production?

Mr. VENTER. Well, thank you very much for your question and your kind comments.

Ms. ESHOO. Thank you.

Mr. VENTER. It is an exciting time in this field. So the ability to now write the genetic code, to actually build DNA fragments and put them together to make larger pieces gives us the ability to reconstitute small things, like the influenza virus, very quickly. So as Dr. Fauci said, with H1N1, there was a variation and the H and the N genes that created a new biological response, we think with

these new techniques in less than 24 hours if, as soon as a new virus was detected, we could have new candidates out there that could go into, for example, the new facility that Novartis has built, based on cell lines to much more rapidly and reproducibly produce vaccines that we are in the process of testing that this year and if it is successful, the flu vaccine you get next year could be a result of these new technologies.

Ms. ESHOO. That is exciting. I wish I had an hour to ask you questions but let me ask this of the entire panel, and that is, what recommendations do you have to the Congress on what we should be doing to facilitate the use of synthetic biology in the development of innovative and affordable drugs?

Mr. VENTER. Well, if I can start, I think it is an excellent question. As I said, we probably can't even imagine all the ideas. When I talk to students, I tell them we are primarily limited now by our imaginations. We need to make sure that is a primary limitation as our imaginations develop in these new areas going forward. I think it is a very exciting time that could influence almost every aspect of human life and we want to drive that forward. We want to prevent frivolous uses. It would be tragic if somebody could call in to one of these companies and order Ebola virus via the—just to inadvertently make something to cause trouble and I think the guidelines coming out of NIH are a great step in the direction to prohibit these frivolous uses. So—

Mr. KEASLING. I would like to put a plug in for basic science and foundation of research so a lot of the technologies that we have developed in the applications are based on basic science and funding for basic science. So it continued funding for basic science, I think is an important step in supporting synthetic biology. I would also like to compare and contrast the ease of funding research that is application based versus foundational based. A lot of my work is application based so it was relatively easy to get funding for production of biofuels or for production even of an antimalarial drug for Bill and Melinda Gates Foundation. Much more difficult is to get funding for foundational work, such as the funding we are getting from the National Science Foundation for the Synthetic Biology and Engineering Research Center. This allows us to develop the tools and the technologies so that they are available to any number of problems that might come up. So funding for foundational research, I think, is incredibly important.

Ms. ESHOO. Thank you.

Mr. KAEBNICK. I wonder if you could imagine a hearing around 1952 with John von Neumann and his team of early computer engineers and asking the same sorts of questions. What should we be doing now to fund the applications in computing that will lead to Silicon Valley? So let us move to today. Well, what should we be doing now to fund the future of Silicon Valley, which might also become known as Carbon, Nitrous, and Phosphorus Valley, the elements that comprise life? And it is not, as Dr. Keasling and Venter are saying, only driven by the applications. It is the investment in the basic tools.

Let me give you one very specific example. Consider the manufacturing of silicon wafers, upon which microprocessors are built. Think of the public and private investments over decades, just in

getting better at building silicon wafers and how the entire computing and information technology industries are based upon those foundational investments.

Now let us consider synthetic biology. All of synthetic biology genomics depends on being able to synthesize and construct genetic material, the information and coding molecule that defines life. What is our national strategic initiative at getting better at building DNA? We don't have one. Arguably, you could make the case that genetic material is at least as important as doped silicon going into a computer. So one specific recommendation I add to just basic funding is to look at core strategic priorities that could define the tool kit, powering the next generation of biotechnology, such as a national strategic DNA synthesis and construction initiative.

Ms. ESHOO. Thank you very much.

Dr. FAUCI. Well, thank you for that question, Ms. Eshoo. I would think the committee, at least from a historical standpoint, has been extraordinarily supportive of what we do at NIH. I have testified before this committee many times and its subcommittees and the only thing I ask of you is to continue to do what you do. We will be transparent with you. Do not overregulate something that needs care and responsibility and integrity and work with us in making sure we lay the foundation that that transparency, integrity and responsibility are there. We will try our best but we really rely very much on your support that you have given us over so many years. So thank you for that.

Ms. ESHOO. Thank you.

Mr. WAXMAN. Thank you, Ms. Eshoo.

Ms. ESHOO. Thank you for each of you—thank you, Mr. Chairman.

Mr. WAXMAN. Dr. Burgess.

Mr. BURGESS. Thank you, Mr. Chairman. While there is so many places to go, Dr. Venter, let me just ask you. I think the question that Mr. Pitts was trying to pose to you is would it be possible utilizing your techniques to grow a new pancreas or a pancreatic cell that then could be given to a person with diabetes?

Mr. VENTER. Well, thank you for the question. I am sorry I did not understand that.

Mr. BURGESS. Well, perhaps not that specifically but, as an end—as a goal, with your basic science applied to say the treatment of diabetes, would it be possible to bioengineer, for you to build the software, the lab, that would create a cell that could produce insulin when it was given to a person and have it perhaps reside at their liver and take over the function of a failed pancreas?

Mr. VENTER. Well, it is an excellent question. In fact, the production of insulin was one of the very first biotech products, once these early techniques were developed at Stanford and University of California, San Francisco, to start producing human insulin genetically. People are working on a variety of genetic circuits to see if small units could be built, where you would have the appropriate regulation. People have been doing this electronically. I think this opens the avenue to do genetically.

Mr. BURGESS. Well, correct, because then you have all of the cellular mediators of insulin response and you wouldn't have to rely upon some of sort outside electronic mediated response if you could

actually grow a pancreatic with the antigenicity that would duplicate the person who was receiving it.

Mr. VENTER. But make—let me make it clear. It is not growing a pancreatic cell. It would be making a small circuit that could work maybe within one of those cells—

Mr. BURGESS. Well, let me ask you this—

Mr. VENTER [continuing]. They are so many decades, maybe centuries away from reproducing a human cell—

Mr. BURGESS. Now wait a minute. Fifteen years ago, in 1995, if someone said how long will it take you to get your computer to make a goat virus with your name and address imprinted into it and all the pathogens removed, what would you have estimated as the timeline there?

Mr. VENTER. I actually thought it was going to be a whole lot faster. We feel bad it has taken us so long.

Mr. BURGESS. Well, I do too then. We will rescind the funding then. On the—

Mr. VENTER. It was privately funded then.

Mr. BURGESS. Let me—and that is an excellent point and I—

Mr. VENTER. We got your goat.

Mr. BURGESS. I wish Ms. Eshoo was still here. The—what you guys are capable of doing with private funding, without government interference, I mean, I shudder to think what computers would look like if we had been in charge of developing those silicon wafers but that is a separate story. On the issue and I don't know whether to ask this of Dr. Venter or Dr. Fauci, but on the issue of the nefarious activities that might occur, but so much of what I have seen in Congress, we don't actually choose to be nefarious but our uneducated consequences are sometimes extremely pernicious. What if we created the artificial life form, the viral equivalent of the zebra mussel, for example, not particularly pernicious in and of itself, but because it replicates so fast and it is so invasive and tenacious that it clogs up waterways and this sort of thing, what do we have to protect us from say the unintended consequence of one of these experiments gone wild?

Mr. VENTER. It is an excellent question and it is one of the top two questions I get when I am speaking about this topic around the world. People are worried about the unintended environmental consequences and we have now close to a 40 year history with molecular biology, with scientists such as ourselves putting genes from almost every species in the bacteria *E. coli* in the laboratory, with no unintended consequences and the reason for that is that bacteria is designed where it can't survive outside of the laboratory. We have argued this as a key tenet for this new field. We need to design into future genomes the ability to have suicide genes—

Mr. BURGESS. Well, I was going to ask you do you have a killswitch that you designed into it or a blowup protector if I could sure that term.

Mr. VENTER [continuing]. The variety of these to do that exactly. In fact, the exciting part of this is we can now use artificial amino acids so that these organisms could grow only in a very well chemically defined environment and never survive in the environment and I think these are very important aspects of this whole field, that we and others have been pushing for from the beginning. If

we are going to make a synthetic algae, about 40 percent of the oxygen that you and I are breathing right now comes from these algae in the ocean. We don't want to mess up that process.

Mr. BURGESS. Right, we don't want to compete with them. You are correct. Dr. Fauci, last August, you were good enough to talk to me about the following months might hold with the H1N1 virus and not having a vaccine at that point and how to advise people were taking care of patients who might be pregnant and teach schoolchildren. The ability to deliver that vaccine eight weeks earlier because of this type of technique, that would have been significant last August. Would it not?

Dr. FAUCI. Absolutely. As you know from our painful experience that we, at the peak of the time that the virus was at its worst, we were still essentially waiting for the full component of the vaccine. So if we had had an eight week more lead time that the availability of the vaccine would have coincided with the demand, we had a dichotomy between demand and supply that would have actually eliminated that gap.

Mr. BURGESS. Right, as we bore down on the beginning of a school year, which obviously was going to throw another wrinkle into that. Now you brought up and you really didn't expound upon it but—

Mr. WAXMAN. Dr. Burgess, we are going to have votes in around 15 minutes. I wanted to—

Mr. BURGESS. OK. I would point out to the chairman that other members of Congress have been allowed considerable—

Mr. WAXMAN. No, you are absolutely right that we won't have time for everybody.

Mr. BURGESS. But this is an important question. It deals with oversight—

Mr. WAXMAN. Please ask it.

Mr. BURGESS [continuing]. And we did swear the witnesses in.

Dr. Fauci, you brought up the issue of reviews and oversight of the synthetic—as we enter the synthetic era and perhaps you can respond to this in writing offline if it would be helpful, but would you give us the benefit of your wisdom on the direction that oversight of this committee should take in the synthetic era?

Dr. FAUCI. I would be happy to do that in writing but as I mentioned, I think the kind of support that you have given for the oversight mechanisms that we have already been put in place and you are now updating and upgrading the guidelines that are out for public comment, that have come back now to incorporate the synthetic biology aspect of it.

Mr. BURGESS. Would you—

Mr. WAXMAN. Mr.—Dr. Burgess—

Mr. BURGESS [continuing]. Perhaps come before us and talk about that at length?

Mr. WAXMAN [continuing]. It really is not fair to the others because we will have to refuse any time to the junior members and it would not really be fair. Probably will end up on your side. Ms. Castor.

Ms. CASTOR. Thank you, Mr. Chairman Waxman, for calling this very interesting hearing. I would like to thank all of you for your testimony. The work you are doing is fascinating and it is impor-

tant and it is obviously that synthetic biology holds such great promise for Americans, whether it is medicine and health or energy, or the environment.

Dr. Keasling, I would like to ask you some questions. This committee has been working very hard on clean energy technologies and it is our challenge is to make energy clean and affordable and this—and BP's deep water horizon oil disaster has been forced on us really highlights the need for our country to focus on clean energy technologies. I understand that Amyris, a company you founded, used synthetic biology to develop a promising method for reaching these goals using—by producing diesel from sugar cane.

Mr. KEASLING. That is correct.

Ms. CASTOR. Could you tell me how this process works? What advantage did synthetic biology provide in producing this biodiesel that conventional technologies could not?

Mr. KEASLING. Right, thanks for that question. So it is a very simple process. The yeast that we have engineered consumes sugar and turns it into a diesel fuel that the yeast pumps out of the cell and it floats to the top and you skim it off. The way this technology or what enables this is that we took the genes that encode enzymes that would transform the sugar into the fuels. So we take these genes from various different organisms and we put them into brewer's yeast. In fact, we put them into industrial strains of yeast that have been widely used for many decades, so these are safe organisms and the process is very much akin to brewing beer. Now what is so great about this fuel that you get out is that it is extremely clean. It reduces greenhouse gas emission by about 80 percent because it is derived from sugar, which comes from sugar cane and that uses carbon dioxide and sunlight to fix that carbon dioxide and it is very environmentally friendly. It has been certified by the U.S. EPA and it is a very clean fuel. What is more is it actually gives extremely good fuel mileage on a gallon of this renewable energy when it is used even pure in the diesel tanks.

Ms. CASTOR. Are you going to be able to take the next step to jet fuel or—

Mr. KEASLING. That is right.

Ms. CASTOR [continuing]. Smart gasoline?

Mr. KEASLING. In fact, we are working quite extensively on that now, Amyris and at the Joint BioEnergy Institute, using the same synthetic biology techniques to now engineer yeast and E. coli to produce jet fuels.

Ms. CASTOR. And how does it compare to the current diesel fuel that is already available and how well does it work in trucks or other equipment?

Mr. KEASLING. And so we have done extensive testing of this fuel with manufacturers of engines. So Cummins, for instance, has done extensive testing of this fuel and many other manufacturers. We now have alliances with airplane manufacturers and engine manufacturers for airplanes so that we can test these new generation of jet fuels in those engines.

Ms. CASTOR. Is it affordable yet?

Mr. KEASLING. We project that when we are up to the yields we need to be, we can produce this for under \$4 a gallon and of course,

affordability also depends on the competition and so right now that would be nearly affordable.

Ms. CASTOR. Now your production process right now, it is not really—you are doing a lot currently. It is not just a long term goal but you are doing this in Brazil.

Mr. KEASLING. That is correct.

Ms. CASTOR. Why not—why Brazil and why not the U.S.?

Mr. KEASLING. Brazil has some of the cheapest sources of sugar. They also have an infrastructure that is built for producing fuels. Currently, they are producing ethanol. Ethanol is obviously not the best fuel and it can't be used in diesel engines. We can use very similar processes and we are, in fact, refitting those microbes that would normally produce that ethanol to now produce diesel fuel. So we are down manufacture—building facilities that will now manufacture this fuel. But Amyris and the Joint BioEnergy Institute hope that we can do this in the U.S. in the very near term. The way we are starting with this, at least from Amyris' perspective, is by going into Alabama and other states in the south where sugar cane can be grown and doing tests on this and in fact, there is an alliance now in Alabama with the U.S. Air Force to try to study the production of jet fuels.

Eventually, through the technologies that we are developing in the Joint BioEnergy Institute, we will be able to use our plentiful sources of cellulosic biomass, which is primarily sugar and turn that sugar into the same types of fuels.

Ms. CASTOR. Thank you very much.

Mr. WAXMAN. Thank you, Ms. Castor. Mr. Gingrey.

Mr. GINGREY. Mr. Chairman, thank you. I have heard some discussion about how you can in the laboratory in this new technique, synthetic biology, produce genes and even entire genome and then there was some discussion of course about H1N1 and the rapid production of vaccine against that virus and it made me think to ask this question and in fact, I will—I don't know who to ask it of. Maybe you should go in the order of your SAT scores but actually, I will probably ask Dr. Fauci to begin.

Mr. WAXMAN. Maybe we should recognize members on that.

Mr. GINGREY. Well, I may be the last one to speak, Mr. Chairman. But the idea of knowing what is in, let us say, a virus from the DNA perspective, is that more difficult now than being able to take these four thiamine, adenosine, guanine, cytosine, whatever these amino acid payers and be able to put together and form a gene or in fact, in some instances, form a complete genome? But to be able to do that, you really need to know what you are trying to produce.

Dr. FAUCI. Right.

Mr. GINGREY. How difficult is it, Dr. Fauci, and I will ask you first, to know really what is—once you have isolated a virus, is that the tough part?

Dr. FAUCI. Right.

Mr. GINGREY. Knowing exactly, you know, the multiple chains and—

Dr. FAUCI. That is really easy. If you get the naturally occurring virus and you sequence it, you are reading the blueprint of nature. If you want to then sequence components of that, different genes,

it is relatively easy now by common techniques to sequence little genome fragments. You could then take those and stick it into something that will code it to make that protein very easily. The difficulty that was had until now and it is still difficult but before what we are talking about is to take an entire genome of a much bigger length than a little snippet, and to synthesize it based on the blueprint that you see in the computer that was a result of your sequencing it, which was really easy. It was difficult a long time ago but it is really easy right now.

So the microbe that Dr. Venter and I will certainly leave it to him to explain more, that he synthesized was on the basis of a blueprint that nature already told us what that blueprint is. Sometimes when you sequence, there are some mistakes. Unfortunately, for Dr. Venter, there were a couple of mistakes in that sequence that actually lost him a few months, if not longer, but if you get the sequence right, you can then synthesize fragments but now you can synthesize the whole thing and take it and stick it in another bacteria, get rid of its resident genes, and let this new synthetic one start coding.

The real challenge is going to be if you want to do something that is entirely new, is how do you put together the circuitry from gene to gene to do something that nature hasn't been your teacher, hasn't told you how to do it because when you have the sequence, nature has already told you what the right sequence is. You just need to synthesize it. The challenge is that the field is going to be facing is that how do you get those new circuits, and there are a lot of people working on these little circuitries, to figure out how you can then make the optimal organism to do optimally with what the panel members were talking about.

Mr. GINGREY. Dr. Fauci, thank you and the minute that I have left, maybe one of the other panelists would also like to comment or elaborate on that same question.

Mr. VENTER. I don't think I can improve on Dr. Fauci's answer.

Mr. GINGREY. Anybody else.

Well, that is great, Mr. Chairman. In the interest of time and my other colleagues, I will yield back the 44 seconds. Thank you very much, Dr. Fauci.

Mr. WAXMAN. Thank you, Dr. Gingrey, for being so generous. Mr. Gordon.

Mr. GORDON. Thank you, Mr. Chairman. I want to—I will probably be brief in just echoing Anna's earlier comments about thanks for you bringing this hearing together and about synthetic biology clearly is going to be a major frontier for the 21st century and you are already pioneers in that and we are glad that you are here. We need to continue this conversation and I think the country that is going to lead in innovation of synthetic biology is the one that is going to lead the world in creating jobs, creating wealth for its people, and there is going to have to be a federal partnership in some ways for that early R&D. Other countries are doing it. We are going to have to do it here and we are doing it.

As a matter of fact, Dr. Venter through the Department of Energy, got some of his early funding that way and as a matter of fact, in this new America Competes Act that we are in the process of dealing with now, within the Office of Science and the Depart-

ment of Energy, we are requiring them to develop a plan on how synthetic biology research can be focused on their mission in terms of energy security and environmental cleanup and those sorts of things, which also indicates that there are different pots of money around the federal government doing work here.

Just like we found in nano research, there are 25 different federal agencies dealing with nano, 15 of them providing some resources. So through the National Nanotechnology Initiative, we put up an umbrella to coordinate that. Just last year, we did the same thing with solar, with water, with stem education. So my question is, should we have some type of a coordinating counsel within the federal government to coordinate the funding in synthetic biology and within that, should there also not mandates, but maybe, and not picking winners or losers, but taking some areas of emphasis? So that will be my first question and then I will follow that on something similar.

Anyone wants—Dr. Venter.

Mr. VENTER. Thank you for your comments and your question. I agree with you. I think this technology has a chance to be one of the most important—

Mr. GORDON. Oh yes, yes.

Mr. VENTER [continuing]. Economic drivers for the future.

Mr. GORDON. Sure.

Mr. VENTER. And the only thing I think would be tragic for this country is for something, you know, quite dramatic not to happen with federal funding. Federal funding seems to follow innovations in my view. It seldom leads them. This is a chance to change that as we drive the kind of tools that—

Mr. GORDON. But should we have some kind of a coordinating agency within the federal government, coordinating where the various areas, where NIH, where DOE or other places that are doing research on synthetic biology?

Mr. VENTER. I would defer to others. I am not sure I am qualified to comment on that, whether that would be good or bad.

Mr. ENDY. Very good question, if I could just offer a perspective. One of the characteristics of synthetic biology is just bringing researchers and others together from very different backgrounds and it would strike me as a wonderful opportunity to create some guiding framework or a leading umbrella that would provide the venue for which engineers and scientists, ethicists and others could come together. So, for example, we have a lot to learn from not just electrical engineering and chemical engineering but every type of engineering. We need the benefit of experts at places like NIST, combined with the expertise at NIH and NSF and DOE and everywhere else. And so how are we going to bring those folks together and then bring them together with the emphasis to help us make best decisions upstream of the work as we have done an oK job with in getting started but now need to scale. So I am very positively responsive to the question.

Mr. GORDON. Well, is anybody who is not and, you know, I think we will—I want to try to follow up on that. The other part of that, going back to the earlier discussion about the semiconductor industry and you know, there are—we lead the world in semiconductor production. Eighty percent of our production goes overseas and 75

percent of the jobs and the money stays here in this country and so I think—and a lot of that was from this somatic, the earlier partnership between the federal government and the industry. So one, we could say maybe this coordinating body. Should we also look at that somatic model and see if there should be some—a partnership is created with public dollars, private dollars, and if so, how would you see that being structured?

Mr. ENDY. The short answer is yes. I think the question about how to best structure it deserves some good thought.

If you look at the last 35 years of biotechnology, there hasn't been a tremendous, although at the research level, there has been a tremendous amount of sharing and cooperation. In terms of translating that into commercialization, there is not always as much of that as you might hope to see. So one of the lessons we might take from the emergence of other technology platforms is to create a mixture of partnerships that support, among other things, open technology platforms. Going further than that, I think it really would, at this point, be worth serious consideration and follow up to figure out the best ways to structure things and I don't know that it is going to be a naive one to one mapping of past experiences that worked in other fields. I think biology and the technology built upon biology is new in many ways. So we got to sort it out.

Mr. GORDON. And can the industry—obviously, there are proprietary advantages that folks want but are there some breakthrough areas that everybody needs and that would we want to focus on, you know, on some breakthroughs?

Dr. FAUCI. I would—

Mr. GORDON. Dr. Venter, take it on over to any of you. To get it into the private sector, do you need some kind of fundamental breakthrough?

Mr. VENTER. And I get some excellent questions so the million based pair genome we made cost us a little over \$800,000, just for the chemicals to make it. DNA synthesis is followed well behind our ability to read the genetic code. Your—from how 10 years ago, it cost the taxpayers over three billion dollars to get one of the two first drafts of the human genome. The technology is now enabling that to happen for maybe on the order of \$10,000. If we get the same order of magnitude changes and possibly this year it will go down in order of magnitude, but will really drive it is if DNA synthesis becomes really cheap and there has not been a lot driving that in the recent future. That would be one avenue.

Mr. GORDON. OK.

Mr. WAXMAN. Thank you, Mr. Gordon. Dr. Griffith.

Dr. GRIFFITH. Thank you, Mr. Chairman. I appreciate you calling this. This is extremely interesting to me and I heard Alabama mentioned and that is my state and my district is five and I am the home of a HudsonAlpha Institute and Rick Myers and his team and I can't tell you how nice it is to have you here. We understand how important this is, as an oncologist and certainly, as you are basic scientists and funding, as Congressman Gordon is pointing out, we need to bring our public along, as far as education is concerned. This is mysterious to them, sometimes frightening. It some-

times goes to our culture and we are not sure what we are doing with DNA and recombinant DNA.

The public needs to be brought to speed on this whole area of genomics, which they are not now and so we, in Alabama, or the HudsonAlpha Institute has put together an educational program where we have reached over 60,000 students and 2,500 educators. We have an application on the iPod for iCell and I think when we go to the public to ask for funding, I think it is important that we begin it in the grammar schools and that someone mentioned Silicon Valley and how important it was that this is our next Silicon Valley.

In order for us to fund it and have it accepted into our culture, we need to start educating our young men and women who are in grammar school about the importance of a cell and the cellular anatomy and the things that are going on because what we are really doing, I think, is going back to basics. We are finally able to get to the basics of the cell, knowledge that was not even known when I was being trained as an oncologist. So is there, in your institutions, an educational arm for the layperson? We have started that in Alabama and it is exciting for the students and I was just wondering is that occurring in other areas as well?

Mr. VENTER. If I may go first, that is an excellent question and I appreciate it very much.

There is probably in my entire career nothing that I have seen that gets young people excited more than the notion of combining the digital world with the biological world. I think they are our number one fans in this area. My institute, The Venter Institute, has a public education program. We have a bus that was initially paid for with NIH funds. It is a research laboratory that goes to the middle schools in the Washington Baltimore area. My understanding of education if we don't catch students at that age, they get lost once they are in high school. But expanding such programs, I think, would be a huge part of this, to capture this excitement and make sure we are the number one nation in this field going forward.

Dr. GRIFFITH. Thank you. Yes, sir.

Mr. KEASLING. So through our funding from the National Science Foundation for the Synthetic Biology Engineering Research Center, we actually spent a great deal of time working with K12 students to try to get them into education, to try to understand science, basic science, but also the engineering of biology. We fund part of the iGem competition that Dr. Endy talked about. We have a new program where we bring in at risk high school students, students that wouldn't normally go to college and get them involved in synthetic biology in summer periods and we have a great record, all of them going off to college after that period.

Dr. GRIFFITH. Fabulous. Thank you very much. Yield back, Mr. Chairman.

Mr. WAXMAN. Thank you, Dr. Griffith. Mr. Markey.

Mr. MARKEY. Thank you, Mr. Chairman, very much. I have a cold so I am trying to quarantine myself down here and hopefully this will lead to the discovery of the cure for the common cold. That would be the biggest breakthrough we could make.

Dr. Venter, I know that you want to potentially use these breakthroughs as a way of taking carbon and taking and making it not this terrible thing that is warming the planet but something that is positive. It can be used in constructive ways in our society. Could you tell us a little bit about how you dream, envision these breakthroughs leading to that possibility?

Mr. VENTER. Thank you very much for the question. People have talked—in fact, Al Gore has talked about carbon based fuels being the problem. In my view, they are not the problem. It is the source of the carbon that is the problem. If the carbon comes from CO₂ or indirectly, as Dr. Keasling has said, through sugar, we have a chance to capture back CO₂ that is being produced when we take new carbon out of the ground. There is not existing biology there would be no reason to have organisms involved to do this and pump lots of hydrocarbons. So we need these new tools of modern molecular biology and synthetic biology to get cells to be much more productive, to get to the billion gallon per facility level that is required. So we think this will help take us there.

Mr. MARKEY. Chairman Waxman and I, last year, out of this committee, we moved the piece of legislation that helped to put a price on carbon and to move to its new technological breakthroughs in this area. Do you think that that is the right direction for us to be heading in?

Mr. VENTER. I think it is personally one of the most important aspects that Congress can do going forward. If we are successful and I expect that Dr. Keasling will be and we will be as well, we will start to have replacements for oil, which could drive the cost of oil down. If the cost of carbon doesn't go up in a stepwise component, we will constantly drive ourselves out of business by making oil cheaper.

Mr. MARKEY. But ultimately, you do believe that we can innovate our way out of the problem as long as we give the proper incentives for these new technological breakthroughs flourish in a short period of time.

Mr. VENTER. I am an optimist and a scientist and we have been—I think these new tools are remarkable tools. Also as a scientist though, I view we actually have to prove that so I think the promise is there. We actually have to be able to prove that potential.

Mr. MARKEY. How long would it take for you to do this kind of a thing and how much would it cost, that is to make this transformational breakthrough that turns carbon into a positive rather than a negative?

Mr. VENTER. As we announced last summer, our program with Exxon Mobil, they are putting up 600 million dollars for this initial stage of funding. Three hundred they are using internally for their engineering and 300 to synthetic genomics to try and develop the biology to make this possible. We are talking about facilities potentially the size of San Francisco. These have to be extremely robust things. Our optimistic estimates, it is going to be a decade before there are substantial replacement for gasoline and diesel fuel that is made from CO₂ in the gas pumps.

Dr. FAUCI. I should mention that—

Mr. MARKEY. I should mention that my time is going run out. Dr. Fauci, the notion of synthetically created DNA conjures up images of the classic science fiction movie, *Bladerunner*, where Harrison Ford hunts down synthetically created humans in a smog-bound Los Angeles dystopia set in 2019. Now we are not confronted with that scientific reality right now.

There is a difference between producing a synthetic microbe or bacteria in a more complex organism. But it does raise the question of who plays God and perhaps you could tell us what kind of discussions or programs you have that help to discuss the ethical ramifications of the beginning of this process that we are now walking down in this new pathway?

Dr. FAUCI. Thank you for that question, Mr. Markey. Myself, as a scientist, my view of what I am seeing right here now is to emphasize what you yourself said. We are talking about a microbe, a bacteria with a one million base pair, not a three billion base pair. That is the first thing. The second thing is appropriately, the president himself has, in a letter of May 20 of this year, written to the Commission on Bioethics Panel and he has asked them to review this from a variety of ethical and other issues to lay some report back to him within six months as to what we feel we need to do to examine this very important question that I am sure a lot of people are going to be asking. So we are already on that. The mandate to the Commission has already been given by the president.

Mr. MARKEY. And I thank you so much for that answer, Doctor. That bioethics panel was established after an investigation I conducted of human experimentation, the government using radioactive materials on human beings and that was 1993 and I do think it is important for us to stay current and have this ongoing discussion, while at the same time recognizing that there are tremendous positive aspects to this. So much so that the Vatican actually called this a very interesting breakthrough because there are many positive aspects to the breakthroughs that Dr. Venter and the others are making at this time. So I thank you, Mr. Chairman.

Mr. WAXMAN. Thank you very much, Mr. Markey. The Chair would like to ask unanimous consent that a letter from the ETC Group, Friends of the Earth, and the International Center for Technology Assessment be included in the record. Without objection, that would be the order.

[The information appears at the conclusion of the hearing.]

Mr. WAXMAN. All right. I want to thank you for being here and giving your presentation to us. We are at the dawn of a new age of science and the breakthroughs described today have the potential to some of the most challenging problems we face, including global warming and global pandemics, but like any new scientific breakthrough, it is important it be used with appropriate guidelines and we will continue to monitor your progress and continue our oversight and also to be available to you to help in any way to assist you as you go forward. Thank you very much for being here.

We will—without objection, we will leave the record open and members may submit written questions and have a response in writing for the record. That concludes our hearing. We stand adjourned.

[Whereupon, at 12:04 p.m., the Committee was adjourned.]
[Material submitted for inclusion in the record follows:]

**U.S. Representative Kathy Castor
Committee on Energy and Commerce
Full Committee Hearing on Synthetic Genomics – Opening Statement
May 26, 2010**

- Mr. Chairman, thank you for holding today's hearing.
- In just a week's time we have learned of and are now addressing what may be a significant scientific advancement with the ability to forever change the way a myriad of health and energy issues are addressed.
- We know that scientists have been able to alter DNA for a very long time, so the ability to now modify DNA in larger segments than ever before is certainly worth learning more about.
- I am interested in the potential health care breakthroughs that this research may lead to - increased productivity in vaccine production; anti-viral drugs; and perhaps down the line, development of synthetic bacteria that can attack some of our deadliest diseases.
- I am particularly interested in the environmental impact that this development may propose. The ongoing oil disaster that we've been faced with over the past few weeks forces us to look further into new ways to combat pollution, and to address disasters like what we currently face. I would like to hear more about how this science may be able to break down the pollution caused by oil spills.
- As this new science continues to develop it will be critical to understand the best way to evaluate the costs and the benefits of the ability to synthesize cells. How – and how much do we regulate what is done with this capability?

- I understand that the research underway at the Venter Institute stands alone. In my home state of Florida synthetic biology research has been done at a number of institutions, namely the University of Florida. However, I look forward to seeing other institutions in Florida and across the country become involved.
- I am interested in knowing how the Venter Institute plans to partner with other research institutions nationwide.
- Again, thank you Mr. Chairman for holding today's hearing allowing us to get a better grasp on what this new development will mean going forward.

REPRESENTATIVE EDWARD MARKEY (D-MA)
ENERGY AND COMMERCE COMMITTEE HEARING
Developments in Synthetic Genomics and Implications for Health and Energy
Opening Statement
May 27, 2010

On May 20th, Craig Venter and his colleagues announced a groundbreaking scientific discovery. For the first time, they were able to give a cell new operating instructions by designing, building and inserting a synthetic genome into it. They have upgraded to Cell 2.0.

The science behind their work may be hard to grasp, but the benefits are not. In the near future, synthetic genomics holds tremendous promise as an instrumental tool for creating biomedical innovations. For example, the technologies they have developed will help produce vaccines more quickly and affordably. The poorest people around the world may finally have access to life-saving drugs they need. In the longer term, their technology could help produce fuel for our cars and trucks that uses carbon pollution rather than producing it.

Like the biggest moments in science, their accomplishment is more than just a technological feat. It fundamentally changes our perspective.

While, I look forward to seeing the promises fulfilled from synthetic genomics, we must acknowledge the safety and ethical responsibilities inherent to this scientific discovery. For decades the federal government has policed the development and use of techniques to modify DNA. This must continue as this new technology is further developed. I am encouraged that safety and ethical concerns are a fundamental part of the agenda at the Venter Institute and the National Institute of Health. We must ensure that science and safety go hand-in-hand.



May 26, 2010

The Honorable Henry Waxman
Chairman
Committee on Energy and Commerce
2125 Rayburn House Office Building
United States House of Representatives
Washington, D.C. 20515

The Honorable Joe Barton
Ranking Member
Committee on Energy and Commerce
2109 Rayburn House Office Building
United States House of Representatives
Washington, DC 20515

**Offering Testimony from Civil Society on the Environmental and Societal
Implications of Synthetic Biology**

Dear Representatives,

We are writing on behalf of international civil society organizations who for some years have been engaged in tracking developments in Synthetic Biology and analyzing the societal and environmental impacts of this emerging technological platform.¹ We understand that on Thursday May 27, 2010 the U.S. House of Representatives Energy and Commerce Committee will hold a hearing on recent developments in synthetic biology and its implications for health and energy. We respectfully request that the committee consider the following testimony as a critical contribution to your work on this matter. We also ask that the committee consider holding a further hearing on this matter so that the voices of those in civil society who have long been concerned about the environmental, public health and socio-economic impacts of synthetic biology as a field can be heard in this hearing process.

We note that this hearing comes immediately before another hearing dealing with the unfolding BP oil spill in the Gulf of Mexico. With this in mind, we urge representatives to consider the importance of asking hard questions about the threats of new experimental technologies *before* they are deployed, not after terrible accidents have already occurred.

Wake up call – time for a pause:

Last week, the J. Craig Venter Institute announced the creation of the first living organism with a synthetic genome claiming that this technology would be used in applications as diverse as next generation biofuels, vaccine production and the clean up of oil spills. We agree that this is a significant technical feat however; we believe it should be received as a wake-up call to governments around the world that this technology must now be accountably regulated. While attention this week has been on the activities of a team from Synthetic Genomics Inc, the broader field of synthetic biology has in fact quickly and quietly grown into a multi-billion dollar industry with over seventy DNA foundries and dozens of ‘pure play’ synthetic biology companies entering the marketplace supported by large investments from Fortune 500 energy,

forestry, chemical and agribusiness companies. That industry already has at least one product in the marketplace (Du Pont's 'Sorona' bioplastic), and another recently cleared for market entry in 2011 (Amyris Biotechnology's 'No Compromise' biofuel) as well as several dozen near to market applications. We believe the committee should consider the implications of this new industry as a whole in its deliberations not just the technical breakthrough reported last week. Without proper safeguards in place, we risk introducing synthetically constructed living organisms into the environment, intentionally or inadvertently through accident and worker error, that have the potential to destroy ecosystems and threaten human health. We will see the widespread commercial application of techniques with grave dual-use implications. We further risk licensing their use in industrial applications that will unsustainably increase the pressure of human activities on both land and marine ecologies through the increased take of biomass, food resources, water and fertilizer or displacement of wild lands to grow feedstocks for bio-based fuel and chemical production.

We call on Congress to:

- 1) Implement a moratorium on the release of synthetic organisms into the environment and also their use in commercial settings. This moratorium should remain in place until there is an adequate scientific basis on which to justify such activities, and until due consideration of the associated risks for the environment, biodiversity, and human health, and all associated socio-economic repercussions, are fully and transparently considered.
- 2) As an immediate step, all federally funded synthetic biology research should be subject to a comprehensive environmental and societal impact review carried out with input from civil society, also considering indirect impacts on biodiversity of moving synthetic organisms into commercial use for fuel, chemicals and medicines. This should include the projects that received \$305 million from the Department of Energy in 2009 alone.
- 3) All synthetic biology projects should also be reviewed by the Recombinant DNA Advisory Committee.

On synthetic biology for biofuels - time for a reality check.

Much of the purported promise of the emerging Synthetic Biology industry resides in the notion of transforming biomass into next generation biofuels or bio-based chemicals where synthetic organisms work as bio-factories transforming sugars to high value products. On examination much of this promise is unrealistic and unsustainable and if allowed to proceed could hamper ongoing efforts to conserve biological diversity, ensure food security and prevent dangerous climate change. The sobering reality is that a switch to a bio-based industrial economy could exert much more pressure on land, water, soil, fertilizer, forest resources and conservation areas. It may also do little to address greenhouse gas emissions, potentially worsening climate change.

By way of an example, the team associated with Synthetic Genomics Inc who have recently announced the creation of a synthetic cell have specifically claimed that they

would use the same technology to develop an algal species that efficiently converts atmospheric carbon dioxide into hydrocarbon fuel, supposedly addressing both the climate crisis and peak oil concerns in one fell swoop. Yet, contrary to the impression put forth by these researchers in the press, algae, synthetic or otherwise, requires much more than just carbon dioxide to grow - It also requires water, nutrients for fertilizer and also sunlight (which therefore means one needs land or open ocean - this can't be done in a vat without also consuming vast quantities of sugar).

In order for Synthetic Genomics or their partners to scale up algal biofuel production to make a dent in the fuel supply, the process would likely exert a massive drain on both water and on fertilizers. Both fresh water and fertilizer (especially phosphate-based fertilizers) are in short supply, both are already prioritized for agricultural food production and both require a large amount of energy either to produce (in the case of fertilizers) or to pump to arid sunlight-rich regions (in the case of water). In a recent life-cycle assessment of algal biofuels published in the journal *Environmental Science and Technology* researchers concluded that algae production consumes more water and energy than other biofuel sources like corn, canola, and switch grass, and also has higher greenhouse gas emissions.ⁱⁱ "Given what we know about algae production pilot projects over the past 10 to 15 years, we've found that algae's environmental footprint is larger than other terrestrial crops," said Andres Clarens, an assistant professor in U.Virginia.'s Civil and Environmental Department and lead author on the paper.ⁱⁱⁱ Moreover scaling-up this technology in the least energy-intensive manner will likely need large open ponds sited in deserts, displacing desert ecosystems. Indeed the federally appointed Invasive Species Advisory Committee has recently warned that non-native algal species employed for such biofuel production could prove ecologically harmful and is currently preparing a fuller report on the matter.^{iv}

Meanwhile it is not clear that the yield from algal biofuels would go far to meeting our energy needs. MIT inventor Saul Griffiths has recently calculated that even if an algae strain can be made 4 times as efficient as an energy source than it is today it would still be necessary to fill one Olympic-size swimming pool of algae every second for the next twenty five years^v to offset only half a terawatt of our current energy consumption (which is expected to rise to 16 TW in that time period). That amounts to massive land use change. Emissions from land use change are recognized as one of the biggest contributors to anthropogenic climate change.

Moving Forward - Time for new regulation

The rapid adoption of synthetic biology is moving the biotechnology industry into the driving seat of industrial production across many previously disparate sectors with downstream consequences for monopoly policy. Meanwhile it applying in commercial setting a set of new and extreme techniques whose proper oversight and limits has not yet been debated. It also enables many more diverse living organisms to be produced using genetic science at a speed and volume that will challenge and ultimately overwhelm the capacity of existing biosafety regulations. For example, Craig Venter has claimed in press and in his patent applications that when combined with robotic

techniques the technology for producing a synthetic cell can be perfected to make millions of new species per day.^{vi} Neither the US government nor any other country has the capacity to assess such an outpouring of new synthetic species in a timely or detailed manner. The Energy and Commerce Committee urgently needs to suggest provisions for regulating these new organisms and chemicals derived from them under the Toxic Substances Control Act, Climate Change legislation and other legislation under its purview before allowing their release into the environment. It also needs to identify how it intends to ensure that the use of such organisms whether in biorefineries, open ponds or marine settings does not impinge on agriculture, forestry, desert and marine protection, the preservation of conservation lands, rural jobs or livelihoods.

To conclude, Congress must receive this announcement of a significant new lifeform as a warning bell, signifying that the time has come for governments to fully regulate all synthetic biology experiments and products. It is imperative that in the pursuit of scientific experimentation and wealth creation, we do not sacrifice human health, the environment, and natural ecosystems. These technologies could have powerful and unpredictable consequences. These are life forms never seen on the planet before now. Before they are unleashed into the environment and commercial use, we need to understand the consequences, evaluate alternatives properly, and be able to prevent the problems that may arise from them.

If you have, any questions please contact: Jim Thomas at jim@etcgroup.org or 1-514-273-9994, Eric Hoffman at ehoffman@foe.org, or 202-222-0747, or Jaydee Hanson at jhanson@icta.org or 703-231-5956.

Sincerely,

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ⁱ For an introductory overview of societal issues raised by Civil Society around Synthetic Biology see ETC Group, “Extreme Genetic Engineering: An Introduction to Synthetic Biology” (Ottawa, ON: ETC Group, 2007). Available online at <http://www.etcgroup.org/en/node/602>

ⁱⁱ Andres F. Clarens, Eleazar P. Resurreccion, Mark A. White and Lisa M. Colosi. Environmental Life Cycle Comparison of Algae to Other Bioenergy Feedstocks. *Environmental Science & Technology*, 2010; 100119091456057 DOI: 10.1021/es902838n

ⁱⁱⁱ University of Virginia (2010, January 25). Engineers find significant environmental impacts with algae-based biofuel. *ScienceDaily*. Retrieved May 26, 2010, from <http://www.sciencedaily.com/releases/2010/01/100121135856.htm>

^{iv} NISC note, “Biofuels: Cultivating Energy, not Invasive Species” Approved by the Invasive Species Advisory Committee (ISAC) on August 11, 2009 . Accessed online at www.invasivespecies.gov/home_documents/BiofuelWhitePaper.pdf

^v Saul Griffith’s presentation to the Long Now Foundation “Climate Change Recalculated” available online at <http://www.longnow.org/seminars/02009/jan/16/climate-change-recalculated/>

^{vi} For Venter’s claim see US Patent Application US20070264688A1: “Synthetic Genomes”. For discussion of the implications of this see Jim Thomas, ETC Blog “Synthia gets a Shotgun” accessed online at <http://etcblog.org/2007/12/09/synthia-gets-a-shotgun-goodbye-genetic-engineering/> 9th December 2007.

